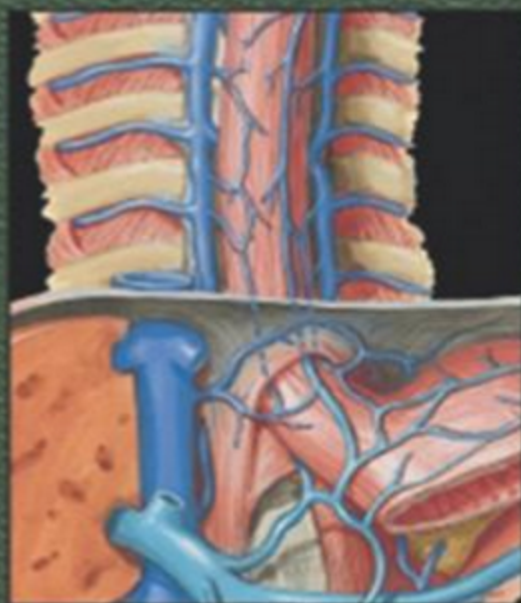


THE NETTER COLLECTION of Medical Illustrations

FRANK H. NETTER, MD 2nd Edition

VOLUME 9



Digestive System

PART I Upper Digestive Tract

JAMES C. REYNOLDS
PETER J. WARD
DAVID A. KATZKA
HENRY P. PARKMAN
MICHELE A. YOUNG



The Netter Collection OF MEDICAL ILLUSTRATIONS **Digestive System** Part I—Upper Digestive Tract

2nd Edition

A compilation of paintings prepared by
FRANK H. NETTER, MD

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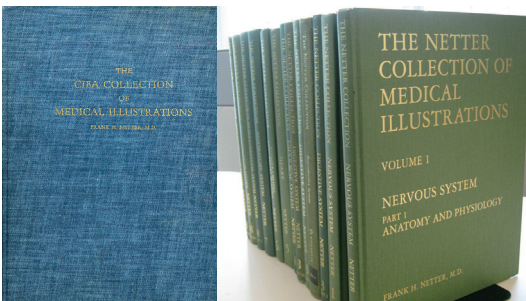
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ABOUT THE SERIES



Dr. Frank Netter at work.



The single-volume "blue book" that paved the way for the multivolume *Netter Collection of Medical Illustrations* series affectionately known as the "green books."

Dr. Frank H. Netter exemplified the distinct vocations of physician, artist, and teacher. Even more important—he unified them. Netter's illustrations always began with meticulous research into the detailed human clinical anatomy and pathology, a philosophy that steered his broad and deep medical understanding. He often said: "Clarification is the goal. No matter how beautifully painted, a medical illustration has little value if it does not make clear a medical point." His greatest challenge and greatest success was charting a middle course between artistic clarity and instructional complexity. That success is captured in this series, beginning in 1948, when the first comprehensive collection of Netter's work, a single

volume, was published by CIBA Pharmaceuticals. It met with such success that over the following 40 years the collection was expanded into an 8-volume series—each devoted to a single body system.

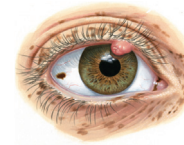
In this second edition of the legendary series, we are delighted to offer Netter's timeless work, now arranged and informed by modern text and radiologic imaging contributed by highly respected neurologic authorities from world-renowned medical institutions, and supplemented with new illustrations created by artists working in the Netter tradition. Inside the classic green covers, students and practitioners will find hundreds of original works of art—the human body in pictures—paired with the latest in expert medical knowledge and innovation and anchored in the sublime style of Frank Netter.

Noted artist-physician, Carlos Machado, MD, the primary successor responsible for continuing the Netter tradition, has particular appreciation for the Green Book series. "*The Reproductive System* is of special significance for those who, like me, deeply admire Dr. Netter's work. In this volume, he masters the representation of textures of different surfaces, which I like to call 'the rhythm of the brush,' since it is the dimension, the direction of the strokes, and the interval separating them that create the illusion of given textures: organs have their external surfaces, the surfaces of their cavities, and texture of their parenchymas realistically represented. It set the style for the subsequent volumes of Netter's Collection—each an amazing combination of painting masterpieces and precise scientific information."

Though the science and teaching of medicine endures changes in terminology, practice, and discovery, some things remain the same. A patient is a patient. A teacher is a teacher. And the pictures of Dr. Netter—he called them pictures, never paintings—remain the same blend of beautiful and instructional resources that have guided physicians' hands and nurtured their imaginations for more than half a century.

The original series could not exist without the dedication of all those who edited, authored, or in other ways contributed, nor, of course, without the excellence of Dr. Netter. For this exciting second edition, we also owe our gratitude to the Authors, Editors, Advisors, and Artists whose relentless efforts were instrumental in adapting these timeless works into reliable references for today's clinicians in training and in practice. From all of us with the Netter Publishing Team at Elsevier, we thank you.

CUSHING'S SYNDROME IN A PATIENT WITH THE CARNEY COMPLEX



Carney complex is characterized by spotty skin pigmentation. Pigmented lentiginos and blue nevi can be seen on the face—including the eyelids, vermillion borders of the lips, the conjunctivae, the sclera—and the labia and scrotum.

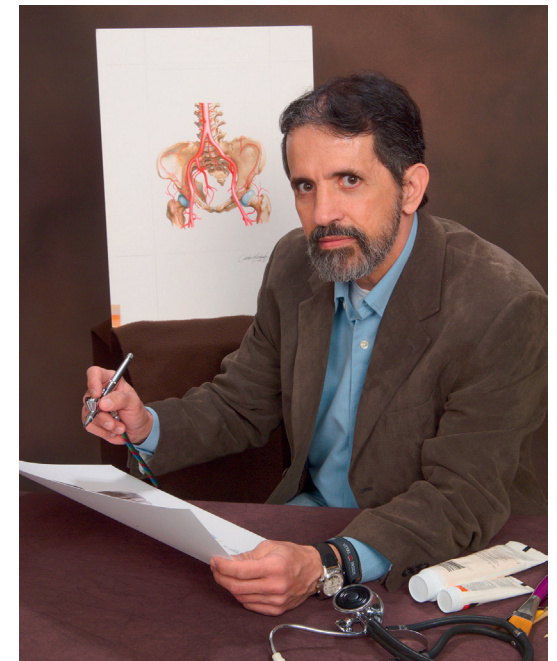
Additional features of the Carney complex can include:

- Myxomas: cardiac atrium, cutaneous (e.g., eyelid), and mammary
- Testicular large-cell calcifying Sertoli cell tumors
- Growth-hormone-secreting pituitary adenomas
- Psammatous melanotic schwannomas



PPNAD adrenal glands are usually of normal size and most are studded with black, brown, or red nodules. Most of the pigmented nodules are less than 4 mm in diameter and interspersed in the adjacent atrophic cortex.

A brand new illustrated plate painted by Carlos Machado, MD, for *The Endocrine System*, Volume 2, 2nd ed.



Dr. Carlos Machado at work.

ABOUT THE EDITORS



James C. Reynolds, MD, Editor, is professor of medicine and the June F. Klinghoffer Distinguished Chair of the department of medicine at Drexel University College of Medicine in Philadelphia.

Dr. Reynolds, a native of Florida, graduated from Florida State University and received his medical degree from the University of Florida, where he was president of his class and received several honors, including admission to Alpha Omega Alpha as a junior, the John B. Gorrie Award as the student with best promise for outstanding future performance, as well as research awards. He completed his residency at Cornell University at New York Hospital and Memorial Sloan Kettering Cancer Center. He then completed a 3-year fellowship at the Hospital of the University of Pennsylvania. He joined the faculty at the University of Pennsylvania, where he became program director and associate chief of the division. He remained funded by the National Institutes of Health (NIH) and other national organizations for his research into the effect of neuropeptides on gastrointestinal motility. In 1990 he became chief of the division of gastroenterology, hepatology, and nutrition at the University of Pittsburgh, where he was a tenured associate professor of medicine and cell biology. He was co-director of the Centers for Digestive Health and an associate professor of medicine and cell biology. In 1996 he became professor of medicine with tenure and chief of the division of gastroenterology and hepatology at MCP Hahnemann University, now the Drexel University College of Medicine. He held this position and that of program director from 1996 to 2008. In those 12 years he held numerous leadership roles in the hospital and college of medicine. He was elected vice-president of the university physicians practice plan (Drexel University

Physicians) and served in this role from 1999 to 2007. From 2006 to 2008 he served as president of the medical staff at Hahnemann University Hospital and was a member of the board of directors of the hospital. He became interim chair of medicine in 2002. In 2005 he was named the June F. Klinghoffer Distinguished Chair of the department of medicine. As Chair he has led the department to a fivefold increase in clinical billing while doubling faculty size and extramural research income. The department continues to receive accolades for its support of exceptional quality and transplantation outcomes and for the national recognition of several divisions.

Dr. Reynolds is a member of the editorial board of *Digestive Diseases and Sciences* and is a reviewer for many other journals. He has published over 100 manuscripts in peer-reviewed journals and has coedited five books. He has received numerous honors including Phi Beta Kappa, AOA, and “Physician of the Year” in 1995 by the Greater Pittsburgh Chapter of the Crohn’s and Colitis Foundation of America, and has been recognized as the most outstanding gastroenterologist in Pittsburgh on two separate occasions by *Pittsburgh Magazine*. He has also been named among Philadelphia’s “Top Docs” 10 times by *Philadelphia Magazine*. He has received teaching awards in both basic and clinical sciences from the University of Pennsylvania and Drexel.

Dr. Reynolds is board certified in internal medicine and gastroenterology and hepatology by the American Boards of Internal Medicine. His primary clinical interests are in the early detection and prevention of cancer, complications of gastroesophageal reflux, and gastrointestinal motility disorders.



Peter J. Ward, PhD, Senior Associate Editor, was born in Denver but grew up primarily in Casper, Wyoming, graduating from Kelly Walsh High School in 1992. He attended Carnegie Mellon University in Pittsburgh and graduated with a bachelor of science degree in biology (genetics, biochemistry, molecular biology) with a minor in chemistry in 1996. He first encountered gross anatomy, histology, embryology, and neuroanatomy at the College of Veterinary Medicine in 1998. Having found a course of study that engrossed him, he matriculated through these courses at Purdue College of Veterinary Medicine, as well as at the branch campus of the Indiana University School of Medicine. Dr. Ward completed a master’s degree in Dr. Kevin Hannon’s muscle research laboratory and then began a doctorate program in anatomy education under Dr. James Walker. He completed his thesis work in 2005—strategies to improve student achievement and recall of medical anatomy—a qualitative and quantitative study.

In July 2005 Dr. Ward joined the faculty of the West Virginia School of Osteopathic Medicine (WVSOM) in Lewisburg, West Virginia. He has taught gross anatomy, embryology, neuroscience, histology, radiography, and the history of medicine. During this time he has also been director of the WVSOM plastination facility, coordinator of the graduate teaching fellows, chair of the curriculum committee, creator and director of a clinical anatomy intensive elective course, host of many anatomy-centered events between WVSOM and the Japan College of Osteopathy and the Atlas College of Osteopathy. Dr. Ward has also served on the council of the American Association of Clinical Anatomists and several of the special interest groups of the same organization. He is also a member of the American Association of Anatomists, American Association for the History of Medicine, and the American Association of Veterinary Anatomists. His research continues to explore how medical students learn effectively, with particular emphasis on anatomy. In conjunction with Bone Clones, Inc., Dr. Ward has been producing a series of tactile models that mimic the feel of anatomical structures when intact and when ruptured during the physical examination. He enjoys exploring the use of video and other media as a supplementary resource in medical education. These videos are available to view at Clinical Anatomy Explained! on YouTube.



David A. Katzka, MD, Associate Editor, is a professor of medicine and head of the esophageal interest group at the Mayo Clinic, Rochester, Minnesota. He attended the Mount Sinai School of Medicine, where he also completed his internship and residency followed by fellowship at the Hospital of the University of Pennsylvania. During his 27 years in Philadelphia he rose to the level of professor of medicine at the University of Pennsylvania. He spent years studying esophageal diseases, first with Dr. James Reynolds and Sidney Cohen and then Dr. Donald O. Castell. Included among his awards are the Louis Duhring Award for the Outstanding Specialist at the University of Pennsylvania and the Distinguished Clinician Award by the American Gastroenterological Association. He has published over 200 peer-reviewed articles, chapters, and editorials with research interest in eosinophilic esophagitis, esophageal motor disorders, Barrett's esophagus, and gastroesophageal reflux disease.



Henry P. Parkman, MD, Associate Editor, received his bachelor's degree from Harvard University and his medical degree from Case Western Reserve University. He completed residency training at Johns Hopkins Hospital and a gastroenterology fellowship at the Hospital of the University of Pennsylvania under the direction of Dr. Sidney Cohen and Dr. James Reynolds, along with GI research training at the Mayo Clinic. Since joining the faculty of Temple University School of Medicine in 1990, Dr. Parkman has been actively involved in studying GI motility at both the basic science and clinical levels. His clinical focus has been on treating patients with GI motility disorders, primarily gastroparesis. Through his research and clinical endeavors, he has developed a number of collaborations with colleagues in gastroenterology, nuclear medicine, surgery, pathology, physiology, and the school of pharmacy.

Dr. Parkman is currently a funded member of the NIH Gastroparesis Clinical Research Consortium, established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to enhance the understanding of gastroparesis. This research has better defined the syndromes of diabetic and idiopathic gastroparesis, and the Consortium is conducting clinical trials to improve the treatment of patients with refractory symptoms of nausea and vomiting.

Dr. Parkman is in charge of Temple's GI motility laboratory, which assesses GI motility dysfunction in patients. The clinical lab has developed expertise in a comprehensive array of GI motility tests for clinical evaluation of patients, including specialized tests of esophageal and gastric motility. Temple is a referral center for evaluation and treatment of GI motility disorders.



Michele A. Young, MD, Associate Editor, is a clinical assistant professor of medicine and the director of the GI fellowship program at the University of Arizona School of Medicine–Phoenix and the associate chief of medicine in gastroenterology at Phoenix VA Medical Center. Before entering medical school at the State University of New York–Stony Brook, she received a master of science degree from the University of Wisconsin–Madison in communication disorders. Dr. Young then worked for several years at Burke Rehabilitation Center in White Plains, New York, as a speech pathologist. She later enrolled in Columbia University School of general studies in the initial pursuit of her medical degree. She completed her internship, residency, and fellowship at the University of Pittsburgh Hospitals. Dr. Young joined the staff as chief of gastrointestinal motility at the Phoenix VA Medical Center and was on the faculty at the University of Arizona School of Medicine–Tucson. She later rose to associate chief of medicine in gastroenterology at the Phoenix VA Medical Center. Dr. Young joined the faculty of the University of Arizona School of Medicine–Phoenix as clinical assistant professor of medicine and program director of the gastroenterology fellowship.

PREFACE

The opportunity to continue to promote the extraordinary educational value of the exquisite art of Dr. Frank Netter in a state-of-the-art update of this classic series has been an honor for me and my esteemed associate editors. Netter's images have brought insightful value to students for over 6 decades and have now been updated and enhanced to benefit future generations of students. This updated edition of *Digestive System* has been rewritten and renewed to include cutting-edge science and state-of-the-art endoscopic, pathologic, and radiographic images, along with Netter's ageless drawings and images that provide insights that foster students' and practitioners' understanding of the anatomy, physiology, and pathophysiology of all eight regions that make up the fascinating and complex digestive system.

Frank Netter, MD, described by the *Saturday Evening Post* as the "Michelangelo of Medicine," continues to be an icon in medical education. The insightful imagery of his medical illustrations provides value for students at all levels of experience who seek insights into the structure and function of digestion in ways that few other texts have in the history of medical education. His vision for these texts—integrating factual information with visual aids—provides unparalleled insights. While born at the onset of the twentieth century, his background mimics many modern medical students—beginning his education in the arts before becoming a scientist. By following his mother's wishes to move beyond art and into medicine, Frank Netter used his passion and brush to communicate the science and the art of medicine in unparalleled ways. In distinction to anatomy texts that offer images of structure only, Netter's paintings also brought incredible insights into the pathophysiology of disease. Just as important, in ways unsurpassed by any other text, he and his dedicated disciples have illustrated how patients are affected by the suffering caused by disease. In all three of these revised parts of *Digestive System*, new artists, committed to the style and value of Dr. Netter's illustrations and led by Carlos Machado, MD, have modernized both the science and the art of his illustrations in all aspects of the digestive system.

This update of the digestive system's anatomy and disease has taken a new approach to communicate the

complexity and integrated beauty of this fascinating organ system. The classic images Dr. Netter drew were preserved whenever possible and altered only as necessary. Dozens of modern radiographic and endoscopic images have been added to all sections in all volumes. The first section in both Parts I and II summarizes shared aspects of the digestive system. Each subsequent section is dedicated to a specific organ and reviews normal anatomy and physiology, pathology, pathophysiology, and disease presentation and treatment.

Each section has been written by authors who were chosen for their dedication to teaching the fascinating aspects of the digestive system. I had the honor of choosing incredibly distinguished associate editors with whom I have had the pleasure of working throughout my career. In each case they have published expertise in their respective organ system and have demonstrated their commitment to and skill in medical education. Their knowledge and insights bring updated scientific understanding of disease mechanisms and current treatments that will convey understanding of the largest and most complex organ system that is unparalleled by other texts. In each section, Dr. Peter Ward updated each of the subsections on normal anatomy and physiology. He has worked hard to preserve the original pictures of Dr. Netter while ensuring the accuracy of the text based on current terminology and science.

In Part I of this three-part set I sought to provide insights and an overview of the upper digestive tract. Michele Young, MD, associate chief of gastroenterology at the University of Arizona's Veterans Administrative Hospital in Phoenix, has written the first organ-focused chapter on the complex anatomy, physiology, and pathophysiology of pharyngeal and upper esophageal functions. New insights into imaging and physiologic understanding of the complexities of swallowing are provided. David A. Katzka, MD, distinguished professor of medicine at the Mayo Clinic, revised the section on the esophagus, and is clearly one of the world's authorities on the topic. New insights into diseases that are common today but were not known at the time of the first edition, including Barrett's esophagus and eosinophilic esophagus, are beautifully illustrated and discussed. Part I closes with a section by Henry Parkman, MD, a renowned gastric physiologist and

physician from Temple University. Dr. Parkman brings a special new focus on the neurophysiology and electrical physiology of normal gastric function and disease.

I review common anatomic, physiologic, and clinical aspects of intestinal disorders in Section 1 of Part II. In Section 2, Dr. Missale Solomon offers a beautifully written treatment of normal and abnormal disorders of the primary digestive organ, the small intestine. In Section 3, one of modern gastroenterology's eminent educators and Dean at the University of Connecticut, Suzi Rose, MD, discusses the colon.

Part III reviews the normal physiology and pathophysiology of the liver, biliary tract, and pancreas. Grace Su, MD, a distinguished clinician and scientist from the University of Michigan, has exquisitely updated the section on the liver in a way that will bring great insights into this, the largest solid organ in the body. John Martin, MD, another premier physician from the Mayo Clinic, provides wonderful modern images of the biliary tract in Section 2, as well as descriptions of its many associated disorders. Section 3, on pancreatic function and disease, is written by one of the world's premiere scientists and clinicians on pancreatology, Dr. David Whitcomb, chief of gastroenterology and hepatology at the University of Pittsburgh.

I would like to express my gratitude for the talented and dedicated contributors to this wonderful update. First and foremost, thanks must be given to Dr. Netter posthumously for providing the initial version of this text and its wonderful illustrations. I especially want to thank the associate editors and other contributing authors. I also want to thank the amazing artists who work with the publishers, Jim Perkins, Tiffany DaVanzo, Kristen Wienandt Marzejon, and especially Dr. Machado, for their talents and commitment to preserving the magnificent style and imagery of Dr. Netter's drawing. I want to thank my editors at Elsevier, Marybeth Thiel and Elyse O'Grady, for their expertise, patience, and support. Finally, I want to thank my loving wife for more than 4 decades of unwavering support of my efforts to make contributions to the field of gastroenterology, which never ceases to fascinate and challenge me.

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OVERVIEW OF UPPER DIGESTIVE TRACT

DEVELOPMENT OF GASTROINTESTINAL TRACT AT 14 AND 16 DAYS

DEVELOPMENT OF GASTROINTESTINAL TRACT

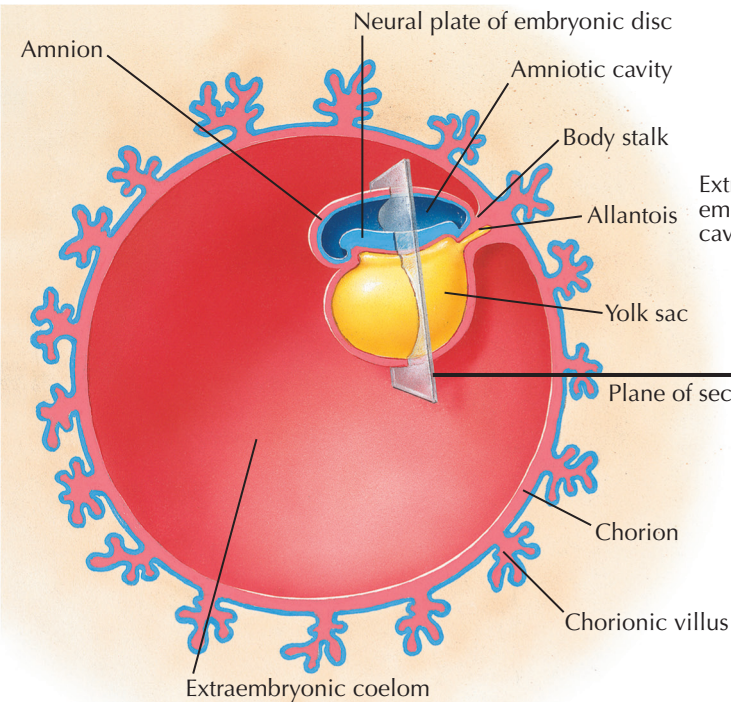
We will take a very short tour of early development prior to the trilaminar embryo stage, at which time we will follow the development of the gastrointestinal tract in detail. Thereafter, for each region of the gastrointestinal tract, we will begin with a short summary of the specific embryology relevant to the structures in that region. The single-celled *zygote* begins dividing roughly 30 hours after an oocyte is fertilized by a spermatozoa. It continues dividing without growing substantially until it reaches the 16-cell stage and is then referred to as a *morula*. The morula consists of an *outer cell mass* surrounding an *inner cell mass*, which will become the *placenta* and the *embryo*, respectively. For the purpose of this section we will focus on the inner cell mass as it morphs to create the body and the organs within.

As the *zona pellucida* (a protective covering of the oocyte and later the *zygote*) gradually disappears, fluid penetrates the morula and creates a space between the inner and outer cell masses. The inner cell mass remains in contact with the outer cell mass in one section, which will eventually form the *connecting stalk* and *umbilical cord*, connecting the embryo to the placenta. The fluid-filled space between the two cell masses is called the *blastocyst cavity* and at this time, roughly 4 days after fertilization, the entire structure is called a *blastocyst*. Normally, the blastocyst implants into the uterine lining starting on the sixth day and further development occurs within.

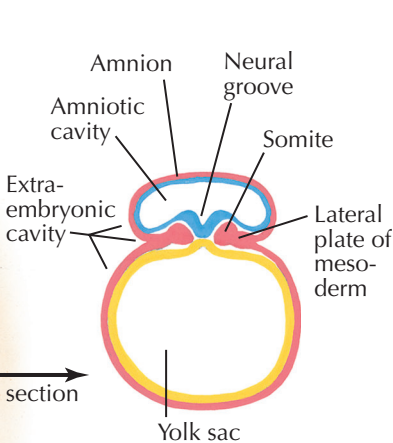
On the eighth day, another fluid-filled space forms between the inner cell mass and the rest of the blastocyst. This is the *amniotic cavity*; despite its small initial size, it will eventually enlarge to surround the entire embryo. The portion of the inner cell mass that is in contact with the amniotic cavity, and amniotic fluid therein, is called the *epiblast*, and the portion that is in contact with the blastocyst cavity is called the *hypoblast*. The epiblast cells are tall columnar cells, and the smaller hypoblast cells appear cuboidal or squamous (flat). The epiblast and hypoblast layers constitute the *bilaminar disc*. By the ninth day, when the blastocyst has fully implanted into the uterus, the blastocyst cavity is referred to as the *primary yolk sac*. Cells that separate the primary yolk sac, bilaminar disc, and amniotic cavity from the developing placenta (cytotrophoblast and syncytiotrophoblast) form the *extraembryonic mesoderm*.

By the 12th day, fluid-filled gaps within the extraembryonic mesoderm converge and form yet another space, the *extraembryonic cavity*, which will compress the primary yolk sac before physically separating it and the bilaminar disc from the rest of the developing placenta

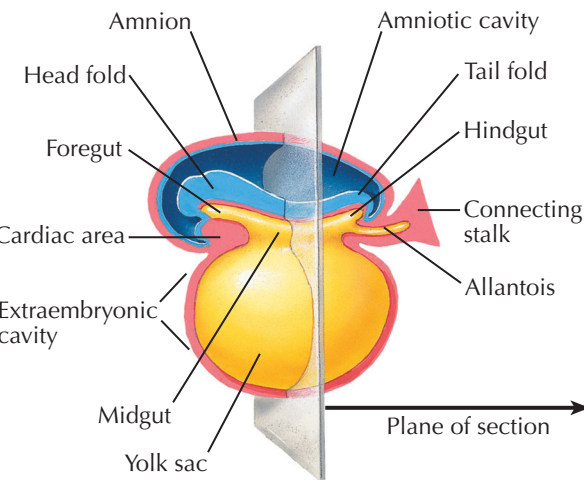
A. 14 days



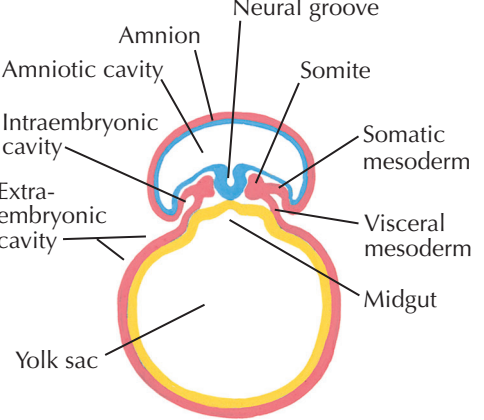
B. Section of A



C. 16 days



D. Section of C



KEY

- Endoderm
- Mesoderm
- Ectoderm

except for a connecting stalk that will eventually become the umbilical cord. As the 13th and 14th days proceed, the primary yolk sac is compressed and pinched in two by the expanding extraembryonic cavity. One small remnant moves away from the bilaminar disc while the larger piece remains in contact with the hypoblast and is now called the *secondary yolk sac*. The secondary yolk sac is lined by cells that are derived from the hypoblast. In one region, these hypoblast cells enlarge and form

the *prechordal plate*, a structure that marks the cranial/superior pole of the developing embryo. Opposite the prechordal plate, epiblast cells begin to proliferate near the embryo's caudal/inferior pole. These cells will form a structure called the *primitive streak*. This will eventually result in the process of *gastrulation*, during which the bilaminar disc is replaced by a *trilaminar disc*. Gastrulation begins on the 15th day and results in the replacement of the epiblast and hypoblast layers by

J. Netter M.D.

DEVELOPMENT OF GASTROINTESTINAL TRACT AT 18 DAYS AND 1 MONTH

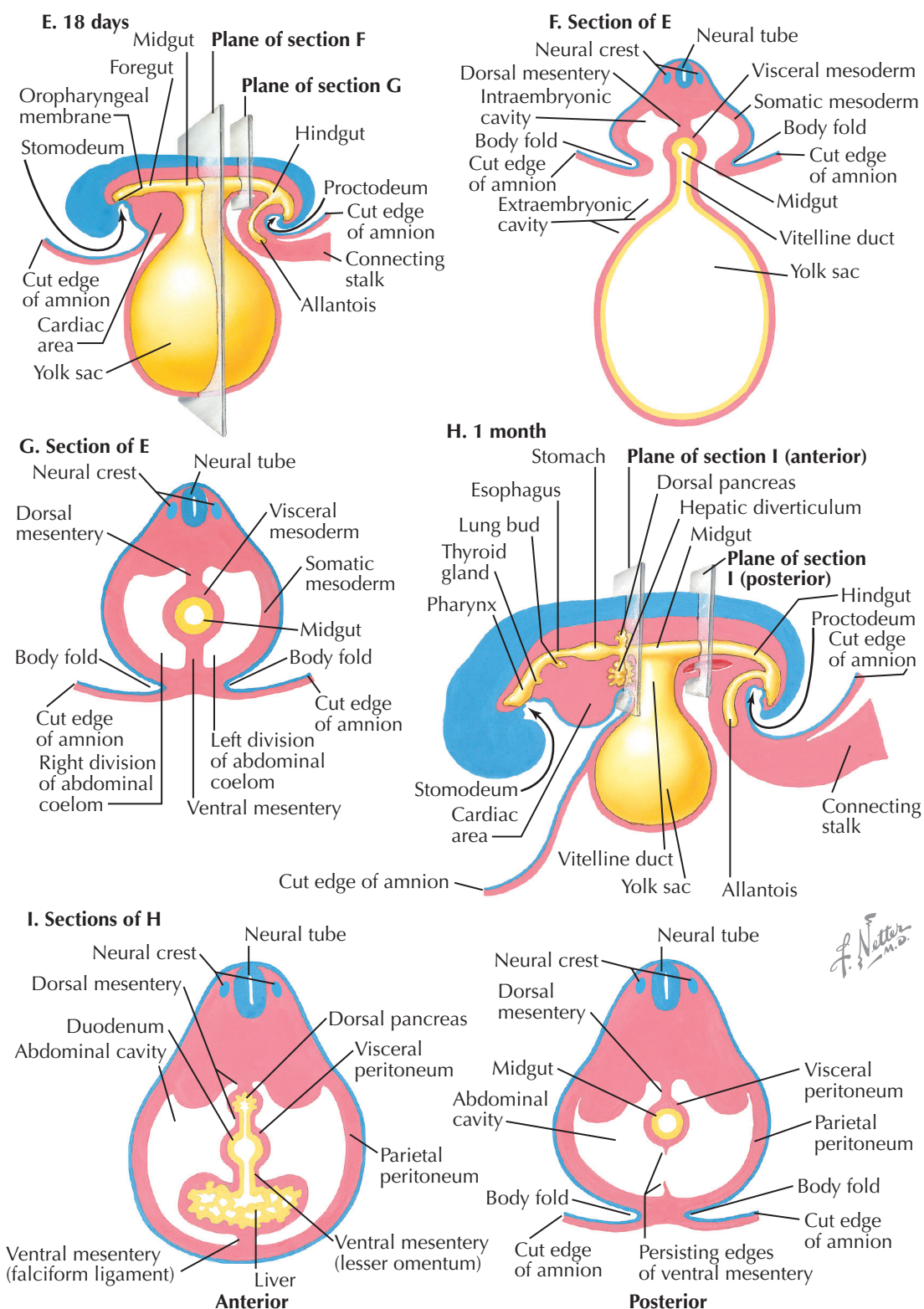
DEVELOPMENT OF GASTROINTESTINAL TRACT

(Continued)

three new germ cell layers, collectively called the *trilaminar embryo*. It consists of the *embryonic ectoderm*, *embryonic mesoderm*, and *embryonic endoderm*. As these layers are referred to hereafter, the word “embryonic” will be dropped.

To form the trilaminar disc, the primary streak extends from the caudal end of the epiblast toward the prechordal plate but does not quite reach it. As it extends cranially, replicating epiblast cells involute into it, invading the space between the epiblast and hypoblast, creating a fissure called the *primitive groove*. This process occurs along the entirety of the primitive streak, but there are some important features that occur at its cranial end, at an area called the *primitive node*. The epiblast cells that migrate through the primitive node migrate between the epiblast and hypoblast layers, moving directly toward the prechordal plate, forming a signaling structure called the *notochordal process*, an important structure in directing further development of the three germ cell layers. As gastrulation proceeds, the hypoblast is entirely replaced by cells that migrate through the primitive streak and settle in contact with the secondary yolk sac. This layer is the endoderm and will produce many of the body's glands as well as the cells that line the respiratory, urogenital, and gastrointestinal tracts. The cells of the former epiblast are now referred to as ectoderm; this layer will produce the epidermis, central nervous system, peripheral ganglia, and other cells of *neural crest* derivation. Between the endoderm and ectoderm is the mesoderm, a layer that will produce the kidneys and gonads, as well as the vascular, muscular, and connective tissue structures of the body. At this stage, we could choose to follow the development of any of the organ systems, but for the purpose of this volume we will focus on the development of the gastrointestinal system. Other systems will be mentioned in a more cursory manner when their development affects the gastrointestinal system.

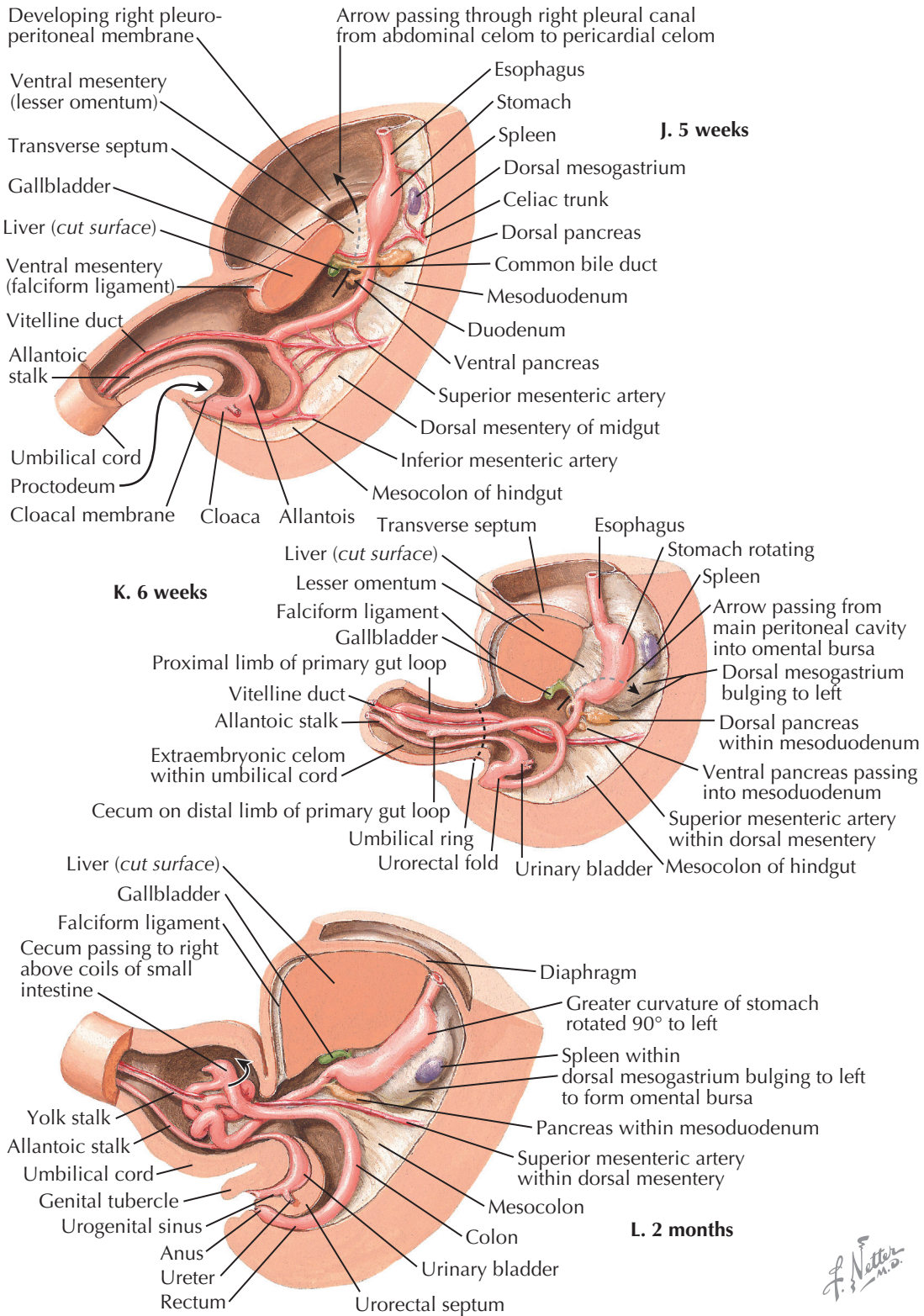
The central region of the ectoderm pinches together to invade the mesoderm and form the midline *neural groove* on the 14th day of development. As development proceeds from the 16th to 18th day, the neural groove pinches together and invades the mesoderm as the *neural tube*, which differentiates to form the spinal cord, brainstem, and cerebral cortex. After the neural tube has detached from the ectoderm, other ectodermal cells, called the *neural crest cells*, migrate into the mesoderm. These cells migrate throughout the developing mesoderm to form the sympathetic chain ganglia, ganglia of the cranial nerves, and postsynaptic parasympathetic ganglia, among others. The mesoderm also undergoes several changes: the *paraxial mesoderm* is



found to the immediate left and right of the neural tube and will form *somites*, which in turn form the axial skeleton, musculature, and dermis. Just lateral to the paraxial mesoderm is the *intermediate mesoderm*, which differentiates into gonads and precursors of the kidneys. Lateral to the intermediate mesoderm is the *lateral plate mesoderm*, which contributes to the body wall, limbs, and connective tissue structures that anchor the organs within the body cavities. In the case of the digestive system, the lateral plate mesoderm forms the abdominal

wall that contains the contents of the *peritoneal cavity* but it also forms the smooth muscle and connective tissues that surround and support the gastrointestinal tract. It also creates the *mesenteries* that connect the digestive organs to the anterior and posterior abdominal wall. As mentioned already, the endoderm forms the *lining* of the gastrointestinal tract and several of the organs that develop from it. We will now describe how the trilaminar embryo morphs to create the abdominal cavity and organs within.

DEVELOPMENT OF GASTROINTESTINAL TRACT AT 5 WEEKS, 6 WEEKS, AND 2 MONTHS



DEVELOPMENT OF GASTROINTESTINAL TRACT
(Continued)

The lateral plate mesoderm is continuous on its lateral edge with the *extraembryonic mesoderm* that surrounds the developing embryo. It is sandwiched by the ectoderm and amniotic cavity dorsally; the endoderm and secondary yolk sac are located ventral to it. At 14 days of development, the lateral plate mesoderm constitutes a single mesodermal region, but shortly thereafter, gaps form within it that create a continuous, horseshoe-shaped space that extends from right to left, going around the cranial end of the embryo. This space is the *intraembryonic cavity*; as it enlarges, it becomes continuous with the *extraembryonic cavity* and it splits the lateral plate mesoderm into two layers. The *parietal (somatic) layer of lateral plate mesoderm* is the more superior of the two and is in direct contact with the ectoderm and amniotic cavity. The more inferior layer is the *visceral (splanchnic) layer of lateral plate mesoderm* and is in contact with the underlying endoderm and secondary yolk sac. This separation is complete but not really dramatic by the 16th day. However, as this space enlarges, it pushes the visceral layer and endoderm medially, creating a notable separation by the 18th day. The visceral layers of lateral plate mesoderm and endoderm on each side grow closer to each other, pinching the endoderm on the left and right, creating a tube that is separate from the rest of the secondary yolk sac. As this proceeds, the yolk sac stretches away from the developing gut tube and remains connected to it via the *vitelline duct* at the midgut, which will form the small intestine and part of the large intestine. Aside from its connection to the vitelline duct and secondary yolk sac, the rest of the endoderm and accompanying visceral lateral plate mesoderm fuse to form a complete tube that stretches from the *oropharyngeal membrane* (developing mouth) to the *cloacal membrane* (eventual anus and urogenital openings). This tube is the early gastrointestinal tract, and it will give rise to all the organs of

digestion as well as the respiratory and urogenital tracts. From cranial to caudal, it is divided into the *foregut* (esophagus, stomach, proximal duodenum, liver, spleen, pancreas), *midgut* (distal duodenum, jejunum, ileum, vermiform appendix, cecum, ascending and transverse colon), and *hindgut* (descending colon, sigmoid colon, and rectum). In addition to the vitelline duct, another pouch of endoderm stretches away from the developing gut tube, the *allantois*. This pouch, originally a caudal

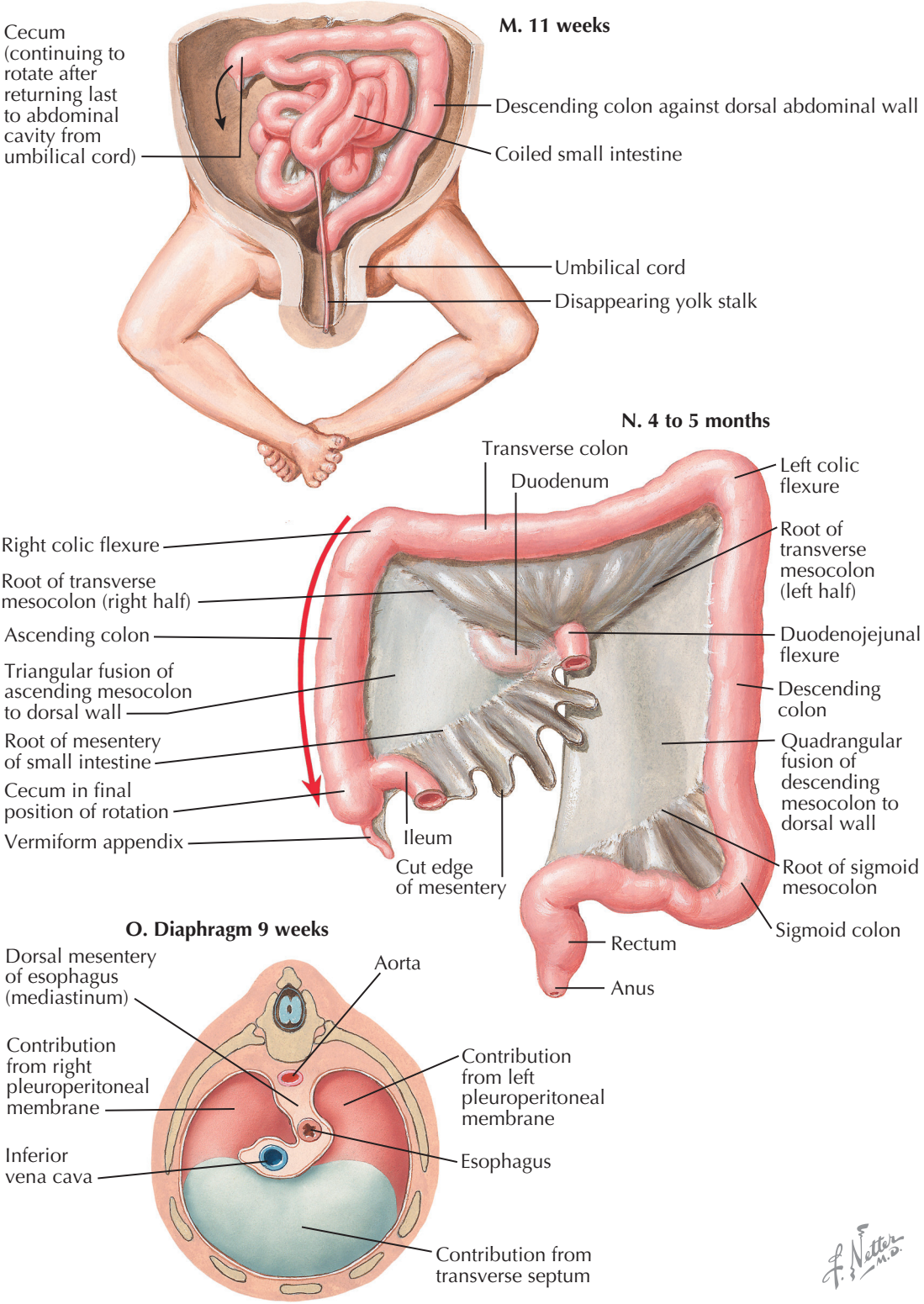
extension of the primary yolk sac, extends off of the developing hindgut, and as development proceeds, it extends into the connecting stalk, cranial to the cloacal membrane. It contributes to the wall of the urinary bladder, but that is not our focus at this time. Eventually both the vitelline duct and allantois will extend alongside each other into the umbilical cord, and aberrations of each structure are associated with malformations of the midgut and urinary bladder, respectively.

DEVELOPMENT OF GASTROINTESTINAL TRACT AT 10 WEEKS AND 4 TO 5 MONTHS; DIAPHRAGM AT 9 WEEKS

DEVELOPMENT OF GASTROINTESTINAL TRACT
(Continued)

While the gut tube is forming from the endoderm and visceral lateral plate mesoderm, a similar process is occurring with the ectoderm and parietal lateral plate mesoderm, so that a left and right lateral fold will form and fuse anteriorly to become the body wall. The left and right lateral folds first extend toward the yolk sac and then turn medially. As this happens, these layers pull the amniotic sac, which had previously covered a small area, to surround the entire developing embryo. Cross sections of the developing embryo at 18 days will appear remarkably different, depending upon whether or not the cross section includes the secondary yolk sac and vitelline duct. A cross section that includes the yolk sac will show an incompletely fused gut tube at the midgut, with the vitelline duct leading away from, and opening into, a ballooned yolk sac. The lateral folds have not yet migrated anteriorly enough to form a complete body wall. However, a cross section in a more posterior plane will exclude the yolk sac and show a fused anterior body wall surrounding a circular gut tube. The gut tube remains anchored to the anterior body wall by the ventral mesentery, which will largely disappear, and the dorsal mesentery, which will remain and transmit the vessels and nerves that connect the gut tube to the rest of the body. The gut tube, with its surrounding visceral layer of lateral plate mesoderm, separates the right and left peritoneal cavities, “descendants” of the intraembryonic coelom to either side. When the ventral mesentery disappears, there will be a single *peritoneal cavity*. By this time, the amniotic cavity almost entirely covers the developing embryo, with only a narrow span of mesoderm separating the right and left lateral folds.

Before 1 month of development has passed, the heart has descended into the thoracic region, bringing along a mesodermal structure, the *septum transversum*, which will contribute to the diaphragm. The septum transver-

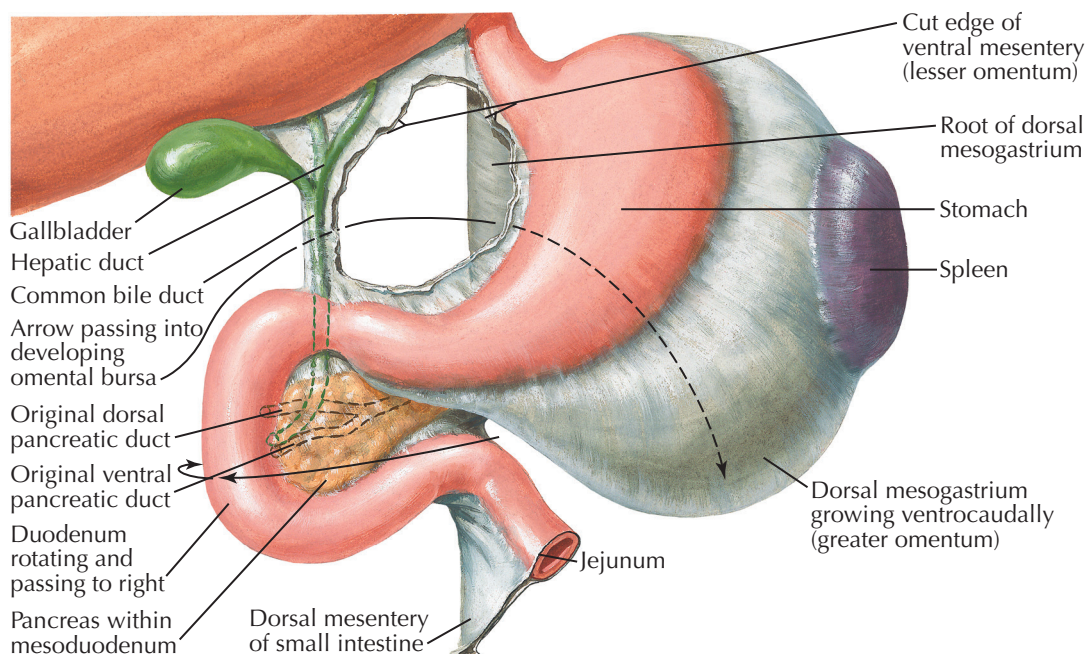


sum narrows the peritoneal cavity considerably, leaving two small openings between the *pericardial cavity* in the thorax and the peritoneal cavity in the abdomen. These are the *pericardioperitoneal canals* and they are normally closed as the diaphragm receives a left and right *pleuroperitoneal membrane* from the body wall. Contributions from the *dorsal mesentery of the esophagus* and muscle from the body wall assist in closing these canals and

creating the diaphragm by the ninth week. Later, the musculature of the diaphragm develops as a secondary ingrowth from the body wall. The phrenic innervation from the cervical spinal cord to the diaphragm originates when the transverse septum first develops at the cervical level of the embryo. As the septum shifts to a low thoracic level, the phrenic nerves elongate. The commonest developmental abnormality of the

RELATIONSHIPS OF STOMACH AT 2 MONTHS; SAGITTAL SECTION AT 2 TO 3 MONTHS

2 months

DEVELOPMENT OF
GASTROINTESTINAL TRACT

(Continued)

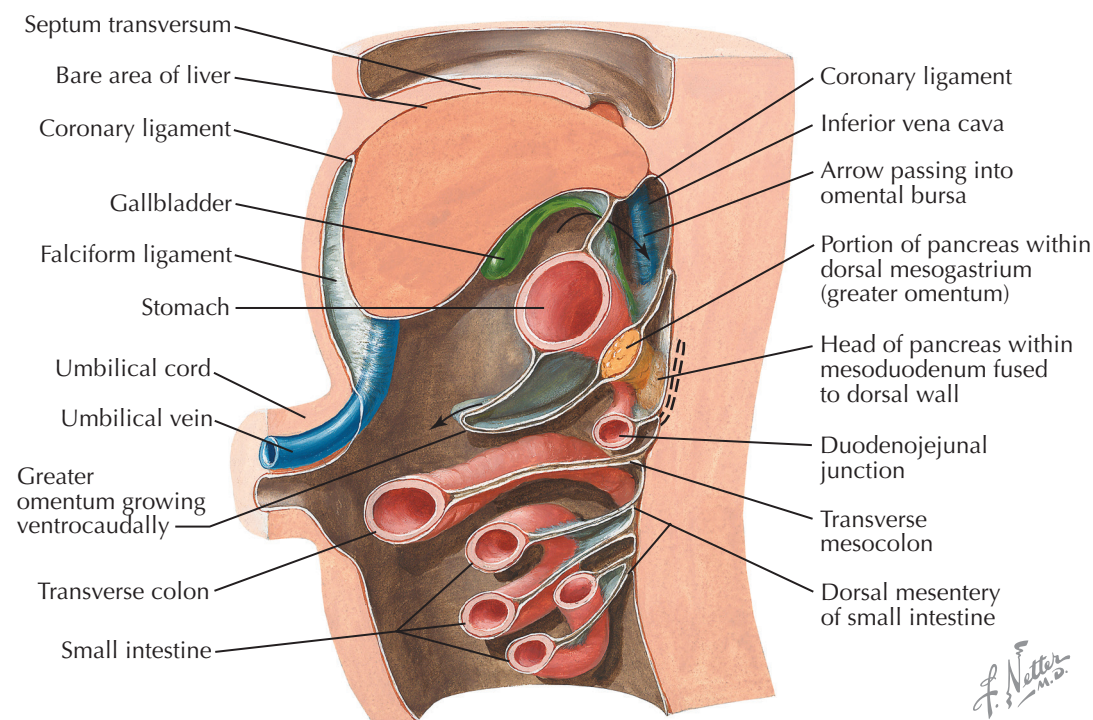
diaphragm is a faulty growth of the left pleuroperitoneal membrane, resulting in an opening through which abdominal viscera may herniate into the left pleural cavity.

Caudal to the developing diaphragm is the foregut. The ventral and dorsal mesenteries remain in contact with the foregut, but the ventral mesentery disappears along the midgut and hindgut, leaving the developing gut tube suspended in the abdominal cavity. From the dorsal aorta, the *celiac trunk* supplies blood to the foregut, and its branches will supply all of the foregut organs as they develop. Extensions of the foregut stretch into the ventral and dorsal mesenteries to create the *hepatic diverticulum* and *dorsal pancreatic bud*, respectively. The hepatic diverticulum will form the liver and gallbladder but will also give rise to a *ventral pancreatic bud*, which will fuse with the dorsal pancreatic bud to form the entire pancreas. The ventral mesentery remains in contact with the developing liver, eventually forming the *falciform ligament*. The further development of this region will be covered in the sections related to the specific foregut organs, the esophagus, stomach, duodenum, liver, gallbladder, and pancreas.

During the sixth week the midgut has begun to elongate substantially and runs out of room within the peritoneal cavity. It moves into the umbilical cord, creating a *physiologic umbilical herniation*, which is a normal event in the development of the gastrointestinal system. The vitelline duct has narrowed but still connects the midgut to the secondary yolk sac, and this connection is one of the reasons that the physiologic herniation occurs, pulling the midgut into the umbilical cord. The vitelline duct will typically disappear roughly 10 weeks into development as the midgut starts returning to the peritoneal cavity. The *superior mesenteric artery* is derived from the vitelline artery and supplies all the developing midgut structures and, eventually, all organs of the midgut. The further development of this region will be covered in the sections related to the small and large intestines.

Development of the hindgut is intimately connected with the urinary and reproductive systems. All three

2 to 3 months



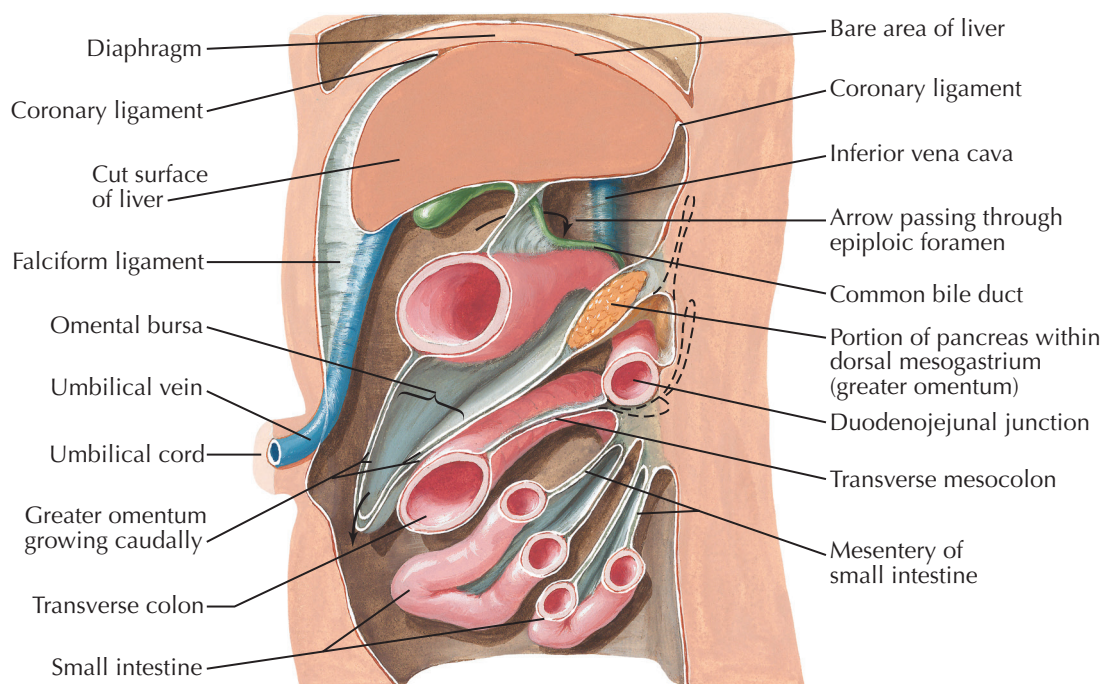
systems initially empty into a common chamber, the *cloaca*, which is separated from the amniotic cavity by a *cloacal membrane*. The allantois extends from the cranial end of the cloaca and stretches into the umbilical cord alongside the vitelline duct. Between 4 and 7 weeks, the mesoderm located between the allantois and the vitelline duct/midgut, called the *urorectal septum*, extends caudally and separates the hindgut from the rest of the cloaca, which will hereafter be called the *urogenital sinus*. By the end of 7 weeks, the urorectal septum has

totally partitioned the digestive and urogenital systems, leaving a *urogenital membrane* and *anal membrane* on the external surface of the body in the place of the cloacal membrane. The *inferior mesenteric artery* will supply all the hindgut organs. The further development of this region will be covered in the sections related to the large intestine and anal regions.

Although the foregut began as a simple, midline, tubular structure lined by epithelium derived from endoderm, it twists, expands, and elongates to create

SAGITTAL SECTIONS AT 3 TO 4 MONTHS COMPARED WITH ADULT

3 to 4 months



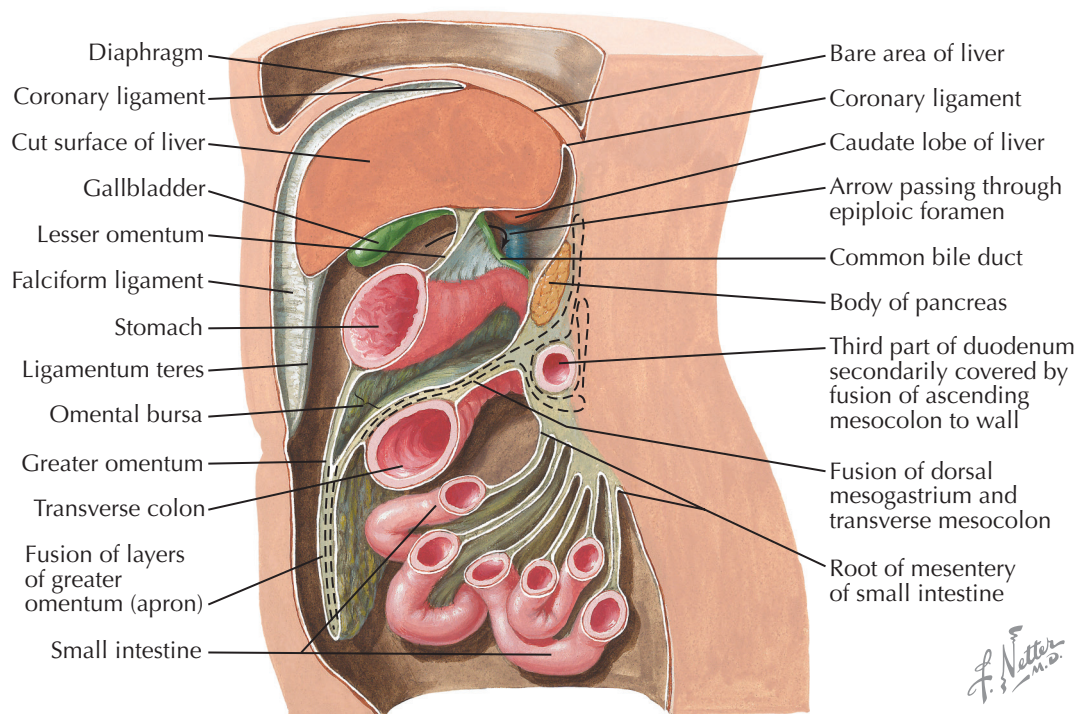
DEVELOPMENT OF GASTROINTESTINAL TRACT

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the adult relationships between each abdominal organ. Fusing and expansion of the dorsal mesenteries are key in this process. The portion of the foregut that will become the stomach first starts to expand in the sagittal plane, ballooning outward on its anterior and posterior surfaces. However, the expansion of the posterior surface quickly outpaces the other side and the stomach begins to bend. The enlarged expansion of the posterior side will become the stomach's greater curvature, and the anterior side will become the lesser curvature. As this is happening, the presumptive stomach rotates so that the posterior side shifts toward the left of the body while the anterior right side shifts to the right. The rotation and expansion of the posterior side are what give the stomach its characteristic shape, with the esophagus entering just to the right of the fundus and greater curvature, and the outlet of the stomach, the pyloric region, shifting to the right and slightly superior to the greater curvature. This moves the stomach from a superior/inferior axis to more of a right/left axis within the abdomen. The inner, circular layer of muscle at the terminus of the stomach enlarges significantly to form the pyloric sphincter.

The rotation and expansion of the stomach do not occur in isolation. The foregut is attached to the posterior body wall by a *dorsal (posterior) mesentery*, called the *dorsal mesogastrium*, in which the *spleen* and dorsal part of the pancreas will develop. The section of this mesentery between the developing spleen and the stomach will become the *greater omentum*. Anteriorly it is connected to the liver, and thereafter, to the anterior body wall by a *ventral (anterior) mesentery*. The section of the ventral mesentery that attaches the liver to the anterior body wall will become the *falciform ligament*, and the section between the liver, stomach, and duodenum will form the *lesser omentum*. As the stomach's posterior surface expands and rotates to the left, the attached mesentery follows, laying the spleen along the left side of the abdominal cavity. The dorsal mesentery between the stomach and spleen expands, folding onto itself and creating a large pocket between the two folds.

Adult relationships



The pocket thus formed is called the *omental bursa*. Continued rotation and expansion of the greater curvature bring this double-layered "apron" to extend inferiorly from the stomach, falling anterior to the transverse colon and small intestine. The motion of the developing stomach and growth of the liver shift the stomach to the left and the liver to the right side of the abdomen. This also brings the omental bursa to lie anterior to the pancreas, inferior to the inferior surface

of the liver, and posterior to the stomach and lesser omentum, which can be subdivided into the *hepatogastric* and *hepatoduodenal ligaments*. Occasionally the omental bursa can extend superiorly and posteriorly to the liver as the *superior recess of the omental bursa*. In its mature form, the omental bursa is isolated from the rest of the abdominal cavity, except for a small opening called the *omental foramen* located immediately posterior to the right edge of the hepatoduodenal ligament.

REGIONS OF THE ABDOMEN

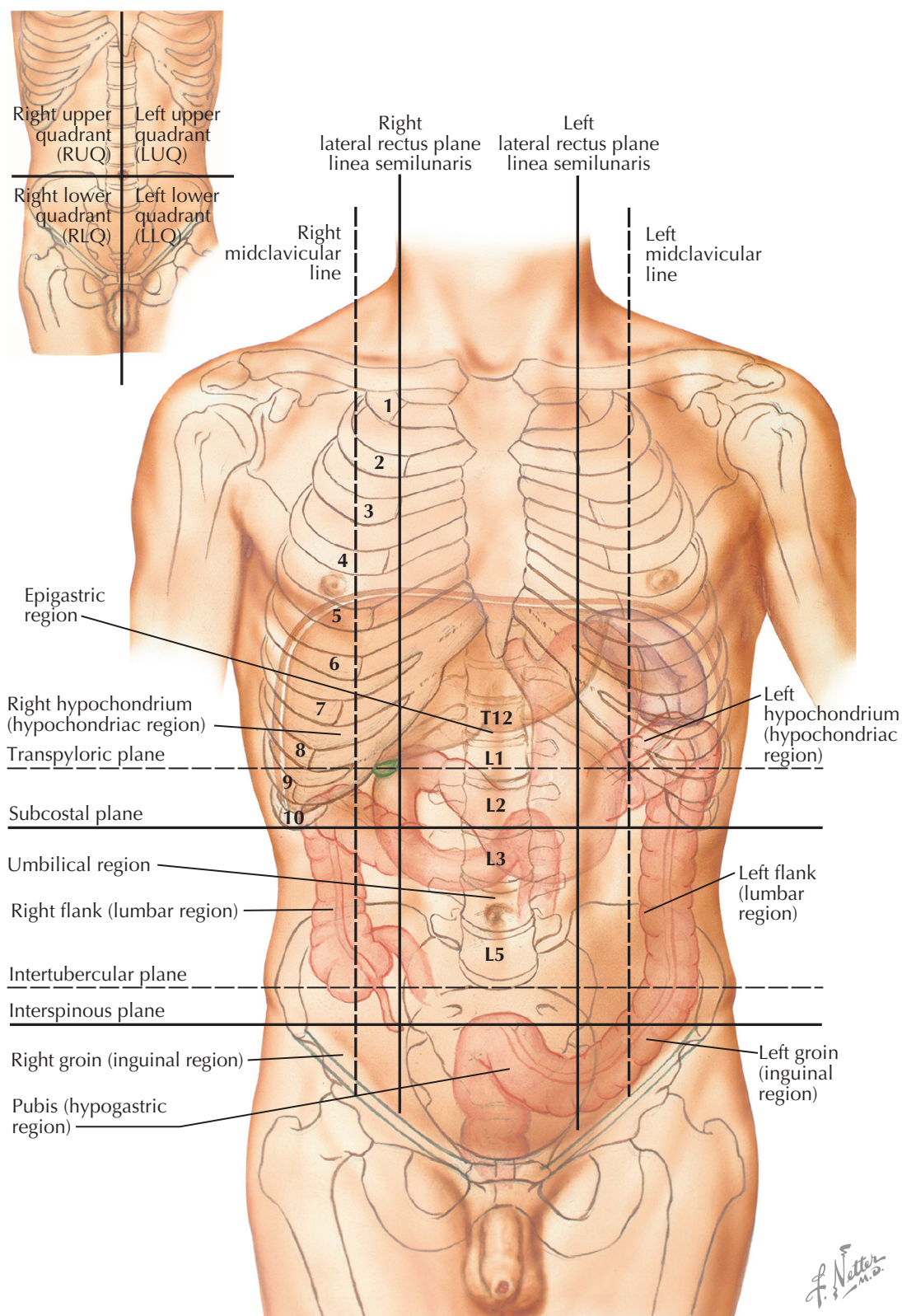
For the sake of convenience, the abdomen is traditionally divided into either four or nine regions. Of these two (somewhat artificial) divisions, the more simple one uses two imaginary planes, one passing vertically and the other horizontally through the umbilicus, dividing the abdomen into *four quadrants*, the right upper, left upper, right lower, and left lower quadrants.

A division of the abdomen into nine smaller areas is accomplished by the use of two vertical and two horizontal planes. The zone above the upper of the two horizontal planes is divided by the two vertical planes into a centrally placed *epigastric region* (epigastrium), with a *right and left hypochondriac region* on each side of it. The zone between the two horizontal planes is divided into a centrally placed *umbilical region*, with a *left and right lumbar region* on each side. The zone below the lower of the two horizontal planes has a centrally placed *hypogastric region* and a *right and left inguinal region*.

Different resources list different landmarks as the basis for drawing the lines of the nine-region scheme. The upper horizontal (superior transverse) line, or plane, may be drawn halfway between the superior border of the sternum and the superior border of the symphysis pubis. This plane has been considered as passing through the pylorus and has thus been called the *transpyloric plane*, which also has been described as being halfway between the xiphisternal junction and the umbilicus, and passing through the tip of the ninth costal cartilage, the fundus of the gallbladder, and the lower part of the body of the first lumbar vertebra. Another way of locating the upper horizontal plane is at the most inferior part of the costal margin (usually the most caudal part of the 10th costal cartilage). This plane is called the *subcostal plane*.

The lower horizontal (inferior transverse) line, or plane, may be assigned to the levels of the tubercles of the iliac crests and is called the *transtubercular plane*; it usually passes through the lower part of the fifth lumbar vertebra, or it may be located at the level of the anterior superior spine of the ilium and called the *interspinous plane*. It has also been located at the highest points of the iliac crests and called the *supracristal plane*.

The two vertical planes, or lines, one on each side, may be located halfway between the median plane and the anterior superior spine of the ilium (or halfway between the pubic tubercle and the anterior superior spine of the ilium or the midpoint of the inguinal ligament; *right and left midinguinal planes*). The other



common way of locating the vertical plane on each side uses the lateral border of the rectus abdominis muscle or the semilunar line, which, if followed inferiorly and medially toward the pubic tubercle, brings the entire inguinal canal into the inguinal region.

In attempting to use either quadrants or the smaller-sized nine regions in the localization of viscera, one finds that a substantial number of individual organs are

not confined to any one region. Attention should be called to the fact that, because the diaphragm is the upper limit of the abdomen, most of the hypochondriac (as the name indicates) regions and parts of the epigastric region are under cover of the ribs. Because these three regions make up a good portion of the right and left upper quadrants, these quadrants also extend well up under the ribs.

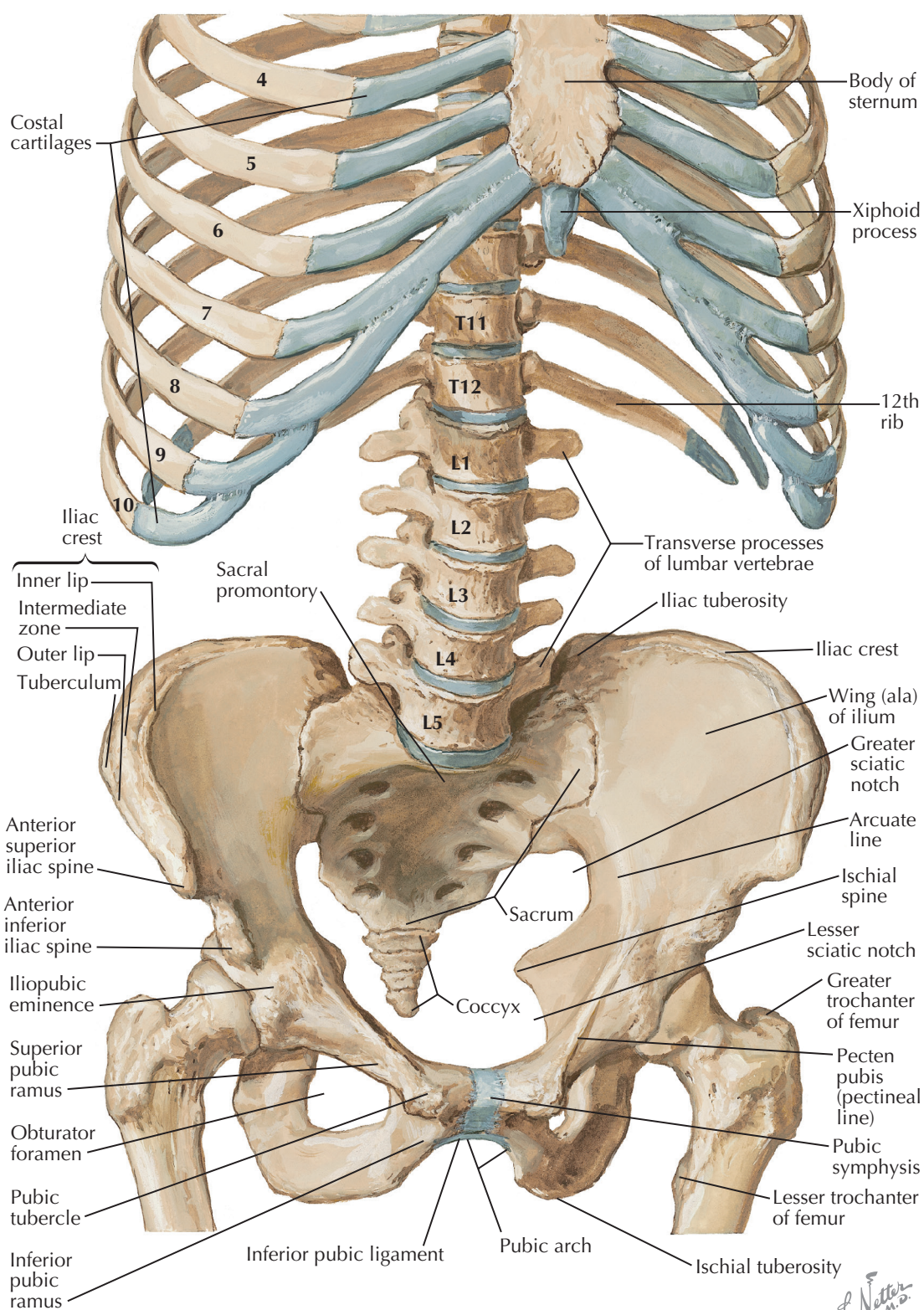
BONY FRAMEWORK OF ABDOMINOPELVIC CAVITY

The skeletal framework that serves as the attachment site for the muscles that make up the abdominal and pelvic walls consists of the lower ribs, costal cartilages, five lumbar vertebrae, and bony pelvis. The costal cartilages of the fifth, sixth, and seventh ribs angle obliquely upward and medially to join the sternum superior and lateral to the xiphoid process. The terminal portion of each of the 8th, 9th, and 10th costal cartilages tapers to a point and is attached to the lower border of the costal cartilage above. The 11th and 12th costal cartilages are quite short, with pointed tips, neither of which attaches to the cartilage above it. The lower border of the 10th costal cartilage is commonly the most inferior part of the caudal margin of the thoracic cage. From the beginning of the 10th costal cartilage to the junction of the 7th costal cartilage with the sternum, a cartilaginous border is formed, which is frequently referred to as the “costal arch” (costal margin), although this term is perhaps more correctly used to refer to the arch formed by the right and left cartilaginous borders as they are connected by the lower end of the sternal body from which the variable *xiphoid process* of the sternum projects. The latter serves as a landmark for the level of the body of the 10th (or 11th) thoracic vertebra.

The five *lumbar vertebrae* present the parts described for a typical vertebral body (centrum) and vertebral (neural) arch, supporting the two transverse processes, the spinous process, and the superior and inferior articular processes.

The bony pelvis is made up of the two hip bones, with the sacrum and coccyx wedged between them posteriorly. For descriptive purposes, the bony pelvis is divided by a plane passing through the sacral promontory and the crest of the pubis, into the major (false) pelvis above the plane and the minor (true) pelvis below this plane. This plane lies roughly in the inlet of the true pelvis, which is bounded by the sacral promontory, crest of the pubis, anterior margin of the *ala of the sacrum*, the *arcuate line of the ilium*, and the *pecten pubis*, all of which could be considered as forming the *linea terminalis*.

The hip bone (os coxae or innominate bone) is made up of the *ilium*, *pubis*, and *ischium*, which are separate bones in the young subject but fuse at the acetabulum in the adult. On the inner surface of the ilium, the arcuate line indicates the inferior border of the ala of the ilium, which ends superiorly in the palpable *iliac crest*, stretching from the anterior superior spine of the ilium to the posterior superior iliac spine. The crest also presents an external (lateral) lip, an internal (medial) lip, and an intermediate line and thickening on its lateral aspect a short distance posterior to the *anterior superior spine*, which is called the tubercle of the crest. The body of the pubis joins the pubic bone on the other side, by means of a fibrocartilaginous lamina, the *symphysis pubis*. The upper border of the body, which is thick, roughened, and turned anteroinferiorly, is called the crest, and at its lateral end is a prominence named the *pubic tubercle*. The *superior ramus of the pubis*, coursing supe-



riorly and posterolaterally, enters into the formation of the acetabulum (acetabular portion, sometimes called the body) and presents a prominent *pecten pubis*, or pectineal line, which is continuous with the *arcuate line of the ilium*. The inferior ramus courses inferiorly and posterolaterally, to join the ramus of the ischium and complete the margins of the obturator foramen. The main portion of the ischium extends inferiorly and posteriorly from the acetabulum, to expand into the *ischial*

tuberosity, which projects posteroinferiorly. From the posterior border of the inner side of the lower part of the acetabular portion of the ischium, the *ischial spine* projects posteromedially between the greater and lesser sciatic notches. A ramus of the ischium courses anteriorly from the lower end of the main portion of the bone, to become continuous with the *inferior ramus of the pubis*, forming what is often referred to as the *ischio-pubic ramus*.

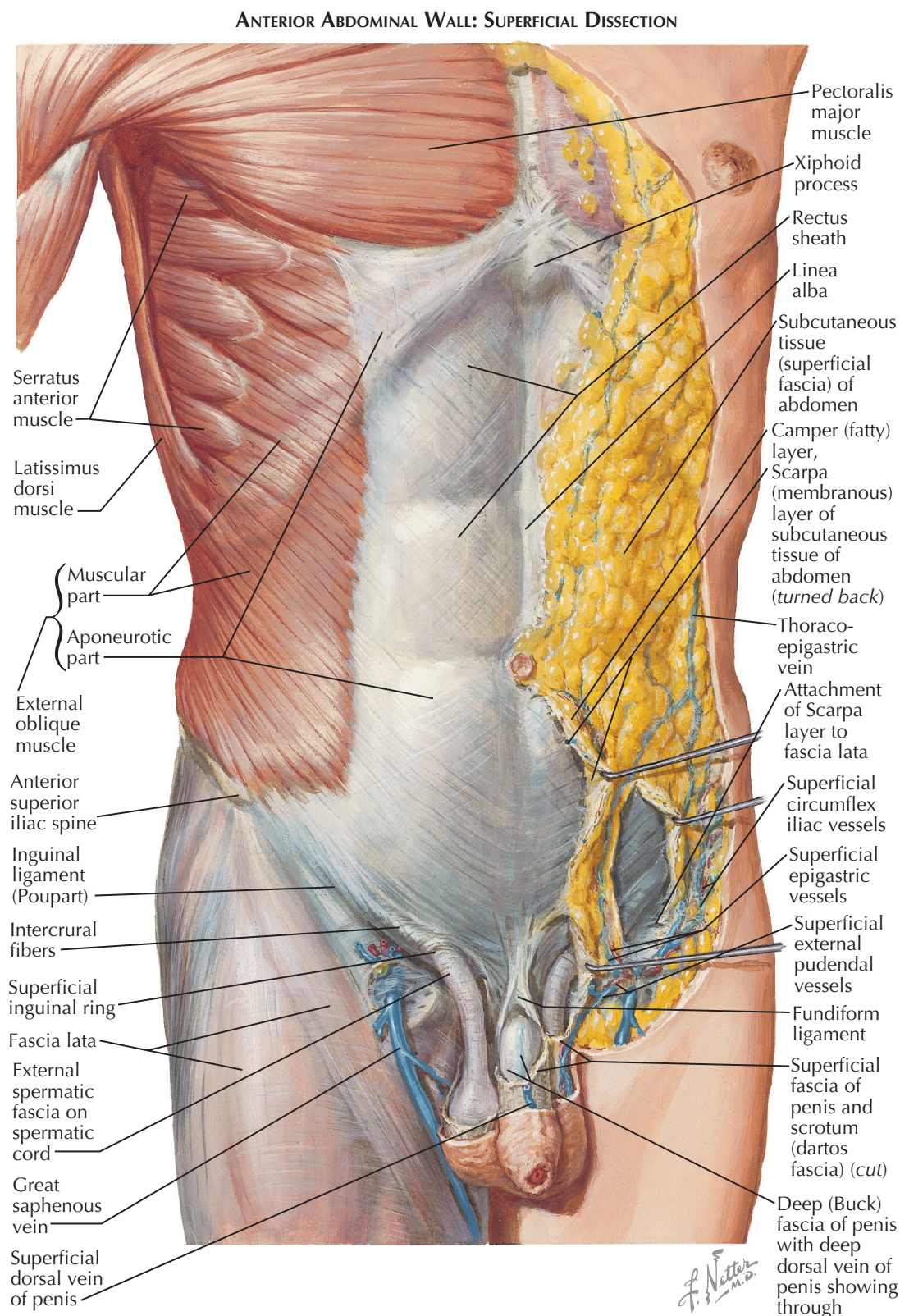
ANTEROLATERAL ABDOMINAL WALL

Before describing the walls of the abdomen, it is necessary to mention different ways in which the word *abdomen* is used. In some cases, abdomen is synonymous with abdominopelvic cavity, but in other cases, it is used in a more specific sense to refer to that portion of the body cavity between the diaphragm and the pelvis minor (true pelvis). Abdomen is also used more loosely to refer to a general region of the body.

For purposes of specificity, it seems advisable to name that portion of the body cavity below the diaphragm the “abdominopelvic cavity” and then to divide this into the abdominal cavity proper and the pelvic cavity (pelvis minor), separated from each other by the plane of the pelvic inlet (the plane passing through the sacral promontory and the pubic crests). It must be remembered, however, that certain structures that are ordinarily referred to as abdominal structures (some of the coils of small intestine, for example) usually hang into the pelvic cavity, and that the inferior and posteroinferior support of the abdominal viscera is furnished by the walls of the pelvic cavity and not by the theoretical plane at the pelvic inlet. It is convenient to divide the borders of the abdominopelvic cavity into four general parts—the anterolateral abdominal wall, the posterior wall of the abdominal cavity, the diaphragm (superior wall or roof of the abdominal and abdominopelvic cavities), and the bowl of the pelvic cavity, which can be loosely called the floor of the abdominopelvic cavity. However, the limits of each boundary are not sharp, because we are dealing with curved contours, and certain arbitrary limits need to be defined for descriptive purposes. This has been done in part above and will be completed as necessary at appropriate places in the following descriptions.

The *anterolateral abdominal wall* fills in the gap in the bony-cartilaginous framework between the costal margin superiorly and the hip bones inferiorly. Following the curve of the body laterally, several muscles, nerves, vessels, and fascial layers will be encountered. For the present work, the quadratus lumborum muscle and the structures medial to it will be included with the posterior wall of the abdominal cavity. Owing to its muscular components, the anterolateral abdominal wall can contract and relax and, thus, help to accommodate the size of the abdominopelvic cavity to changes in volume of the contained viscera and to control intraabdominal pressure. The surgical approach to the abdominopelvic cavity is commonly made through this wall.

Starting from the outside, the layers of the anterolateral abdominal wall are skin, subcutaneous fat (superficial fascia), outer investing layer of deep fascia, the muscles with their related fasciae, transversalis fascia, extraperitoneal fascia, and parietal peritoneum. Abdominal skin is of average thickness (thicker posteriorly than anteriorly and laterally) and rather loosely attached



to the underlying layers, except in the area of the umbilicus.

The *subcutaneous fat* is soft, movable, and contains a variable amount of fat, depending mostly on the state of nutrition of the individual and varying to some extent in distribution. The thickness of this layer can be roughly estimated by picking up a fold, the thickness of which, minus the double thickness of the skin, would be about twice the thickness of the layer. The superficial

fascia, particularly of the part of the wall inferior to the level of the umbilicus, has been classically described as having a superficial fatty layer, called the *Camper fascia*, and a deep membranous layer (to some extent discontinuous), called the *Scarpa fascia*. This classical description is somewhat of a simplification of the actual situation, in which the layering is not always as clear-cut as indicated, but it serves as a means of description if this is kept in mind. The Camper layer is continuous

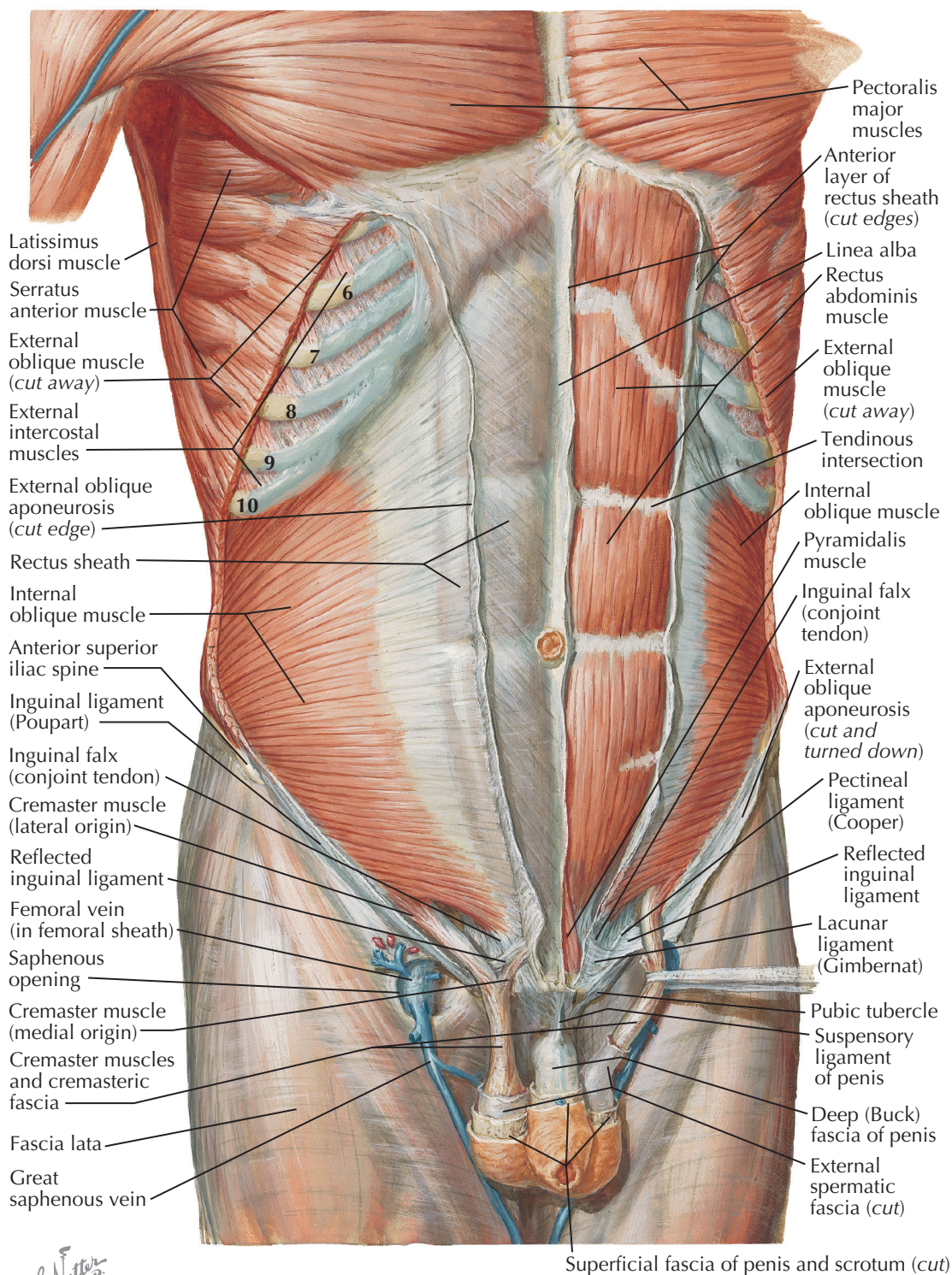
ANTERIOR ABDOMINAL WALL: INTERMEDIATE DISSECTION

ANTEROLATERAL ABDOMINAL WALL (Continued)

with the fatty layer of surrounding areas, such as the superficial fascia of the thigh. The Scarpa layer fuses with the fascia lata along a line parallel to and just inferior to the inguinal ligament. Medial to the pubic tubercle, both layers continue into the urogenital region. This is significant in relation to the path that extravasated urine takes after injuries to the urethra or neck of the bladder. When entering the fasciae in the perineal region, this urine and blood may escape superiorly into the anterolateral abdominal wall. In the male, the two layers continue into the scrotum and blend into a single, smooth muscle-containing layer, the fat being rather abruptly lost as they enter into the formation of the scrotum. Just above the symphysis pubis a considerable addition of closely set strong bands to the Scarpa fascia form the *fundiform ligament of the penis*, which extends down onto the dorsum and sides of the penis.

The outer investing layer of the deep fascia (not readily distinguished from the muscular fascia on the *external surface of the external abdominal oblique muscle* and its *aponeurosis*) is easily demonstrable over the fleshy portion of the muscle but is much more difficult to separate from the aponeurotic portion of the muscle. This layer is attached to the *inguinal ligament* and blends with the fascia coming out from under this ligament to form the fascia lata. It also joins with the fascia on the inner surface of the external oblique at the *superficial inguinal ring* to form the *external spermatic fascia*. External to the inferior end of the *linea alba*, the outer investing layer is thickened into the *suspensory ligament of the penis*, which anchors the penis to the symphysis pubis and the inferior pubic ligament. It is also continuous with the deep fascia investing the penis.

The *external abdominal oblique muscle* typically arises by eight digitations from the external surfaces of the lower eight ribs lateral to the costochondral junction, the middle group of digitations arising at a greater distance lateral to the junction than the ones above and below them. The upper five slips interdigitate with the *serratus anterior muscle*, and the lower three slips interdigitate with the *latissimus dorsi muscle*. The general direction taken by the fibers of this muscle is anteroinferior from their site of origin, and this leads the fibers from the lower two or three digitations to a fleshy insertion on the anterior half of the outer lip of the crest of the ilium, this portion of the muscle having a free posterior border that forms the anterior side of the lumbar triangle. The muscular portion from the remainder of the origin becomes the strong *aponeurosis* of this muscle along a line that courses vertically inferiorly through about the tip of the ninth costal cartilage to the level of the anterior superior iliac spine, where it curves rather sharply laterally to course toward this spine. The aponeurosis passes in front of the rectus abdominis muscle



(where it partly fuses with the aponeurosis of the internal oblique) to blend with the one of the opposite side in the midline linea alba, gaining attachment to the xiphoid process at the upper end of the linea alba and to the pubis at the lower end. The lower margin of the aponeurosis is folded backward and slightly upward upon itself between the anterior superior iliac spine and the pubic tubercle. The folded edge, together with an

extremely variable number of fibrous strands running along it, is called the *inguinal ligament*.

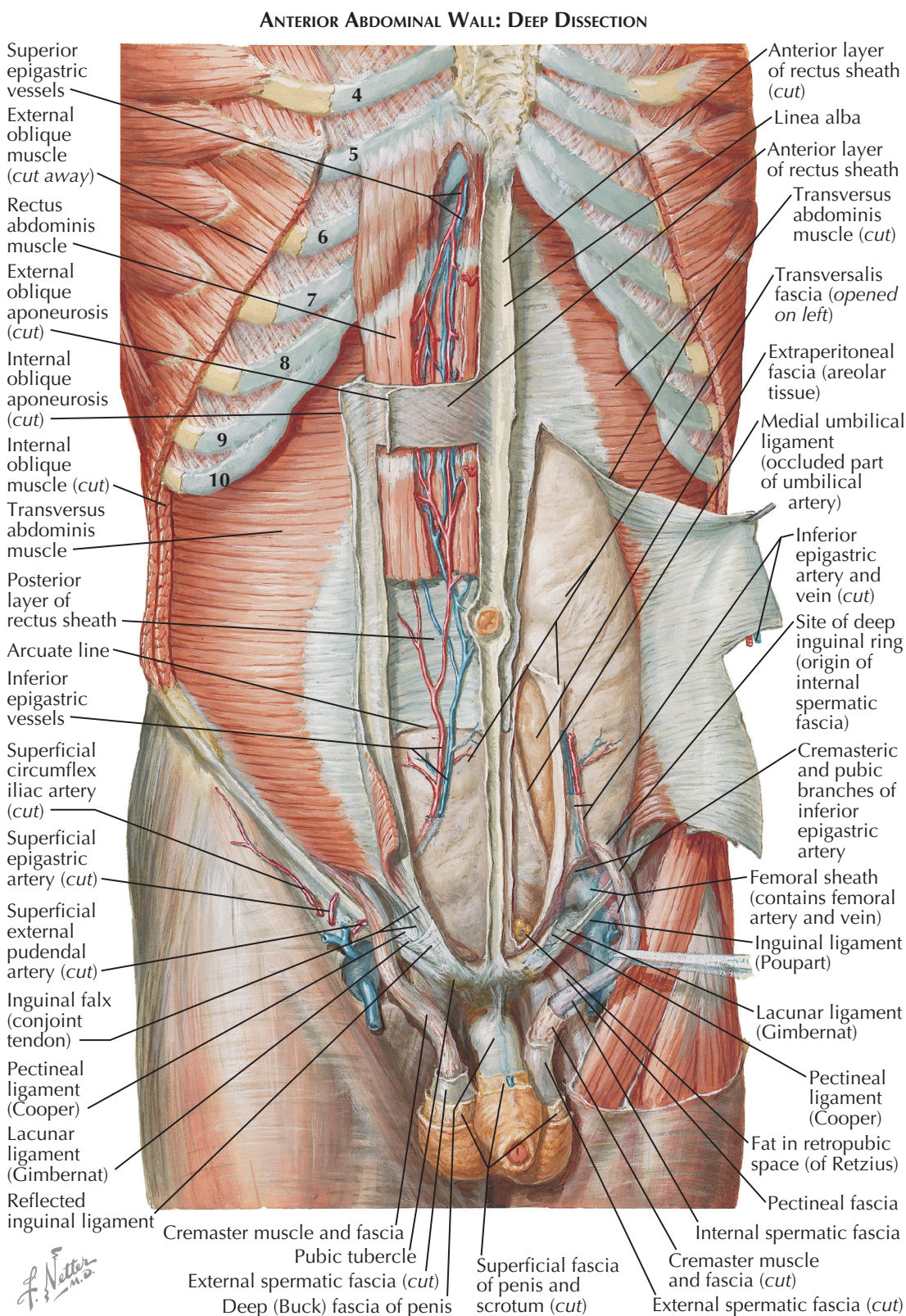
The nerve supply of the external abdominal oblique muscle is derived from the ventral rami of the 6th to 12th thoracic spinal nerves. The 6th to the 11th are intercostal nerves, which continue from the intercostal spaces into the anterolateral abdominal wall to lie in the plane between the internal abdominal oblique and

ANTEROLATERAL ABDOMINAL WALL (Continued)

transversus abdominis muscles. The 12th thoracic nerve is the subcostal nerve, and it follows a course similar to the intercostal nerves above. The iliohypogastric nerve from the anterior ramus of L1 also contributes to the supply. The nerves have a segmental distribution corresponding to the primitive segmental condition of the muscle, with the 10th thoracic extending toward the umbilicus and the 12th toward a point about halfway between the umbilicus and the symphysis pubis.

The external abdominal oblique muscle has several actions in common with the other large muscles of the anterolateral abdominal wall. These are to (1) support the abdominal viscera and, by compressing them, help to expel their contents; (2) depress the thorax in expiration; (3) flex the spinal column; and (4) assist in rotation of the thorax and pelvis in relation to each other. With the pelvis fixed in place, contraction of the external oblique of one side produces a rotation that brings the shoulder of the same side anteriorly.

The *internal abdominal oblique muscle*, smaller and thinner than the external oblique, arises from the posterior layer of the thoracolumbar fascia, from the anterior two thirds or more of the intermediate line (lip) of the iliac crest and the lateral one half to two thirds of the folded-under edge of the external oblique aponeurosis, together with the immediately adjacent and closely related iliac fascia. The majority of the fibers from the thoracolumbar fascia and the iliac crest course superiorly and medially, which means that their direction is perpendicular to the general direction of the fibers of the external oblique. The most posterior fibers insert on the inferior borders of the lower three (or four) ribs and their costal cartilages. The rest of these fibers end in an aponeurosis along a line which extends inferiorly and medially from the 10th costal cartilage toward the crest of the pubis. In the upper two thirds (to three fourths) of the abdomen, the aponeurosis splits at the lateral margin of the rectus into a posterior layer, which passes posterior to the rectus abdominis muscle, and an anterior layer, which passes anterior to it. These two layers join medial to each of the two rectus abdominis muscles and blend with those of the opposite side in the *linea alba*. In the lower one third of the abdomen, the aponeurosis of the internal abdominal oblique does not split but passes entirely anterior to the rectus abdominis muscle to reach the linea alba. The fibers arising from the margin of the external oblique aponeurosis and the related iliac fascia are paler and less compact and course downward and medially, arching superior to the spermatic cord in the male (round ligament in the female). This portion of the internal oblique is generally closely blended with the related portion of the transversus abdominis muscle and tends to fuse with it to create a common, more or less aponeurotic, insertion that passes anterior to the insertion of the rectus muscle on the pubic crest and for a variable distance on the pecten pubis as the *conjoint tendon (inguinal falx)*.



tendon (inguinal falx). The nerve supply of the internal abdominal oblique is by way of the lowest two or three intercostal nerves, as well as the subcostal, iliohypogastric, and ilioinguinal nerves. The actions of the internal oblique are similar to those of the external oblique (see above), except that contraction of the muscle of one side would help to produce a rotation that would bring the shoulder of the same side posteriorly if the pelvis were fixed in place.

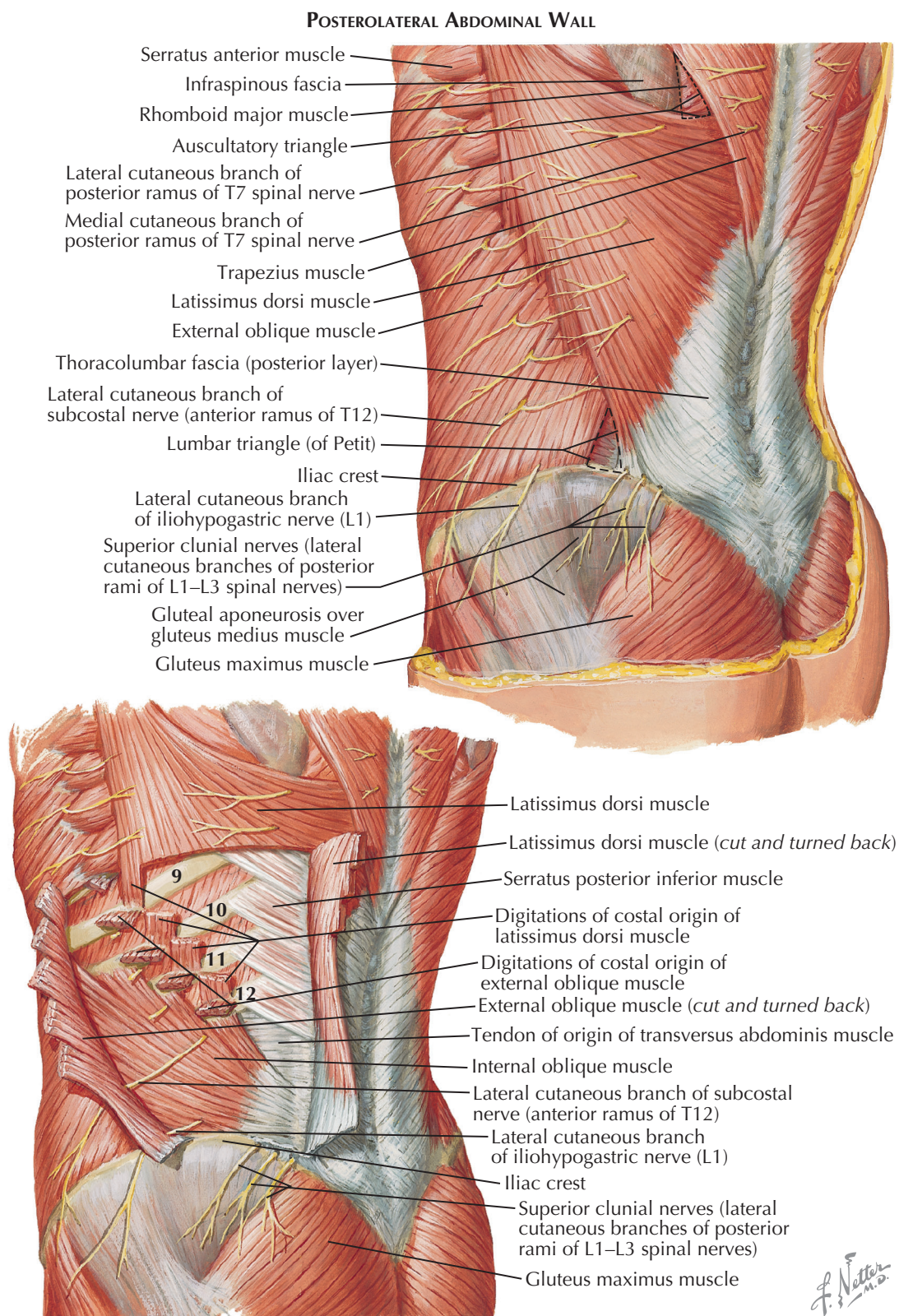
The *cremaster muscle* is well developed only in the male because it is an extension of the lower border of the internal abdominal oblique muscle that travels into the spermatic cord. Laterally it is thicker and fleshier and attaches to about the middle of the turned-under edge of the external abdominal oblique aponeurosis and to the inferior edge of the internal abdominal oblique muscle. From here, the somewhat scattered muscle fibers spread over the spermatic cord along with

ANTEROLATERAL ABDOMINAL WALL (Continued)

connective tissue (*cremasteric fascia*) running between them to end at the *pubic tubercle* and the anterior layer of the rectus sheath. The nerve supply of this muscle is from the genital branch of the genitofemoral nerve and also a branch from the ilioinguinal nerve. The action of the cremaster muscle is to lift the testis toward the superficial inguinal ring.

The *transversus abdominis* is a broad thin muscle that takes a nearly horizontal course around the inner side of the anterolateral abdominal wall. It arises from (1) the inner surfaces of the costal cartilages of the lower six ribs by fleshy slips, which interdigitate with the slips that make up the costal origin of the diaphragm; (2) an aponeurosis formed by the union at the lateral border of the erector spinae muscle of the layer of the thoracolumbar fascia attached to the tips of the transverse processes of the lumbar vertebrae and the layer of this fascia attached to the tips of the spinous processes of the same vertebrae (an indirect origin from the lumbar vertebrae); (3) the anterior one half to three fourths of the internal lip of the iliac crest; and (4) approximately the lateral one third of the folded-under margin of the external oblique aponeurosis and the closely related portion of the iliac fascia. The muscular fibers terminate in a strong (for most of its extent) aponeurosis along a line that extends from deep to the rectus muscle above and courses inferiorly and slightly laterally to emerge lateral to the rectus at about the level of the umbilicus and then to extend variably toward the middle of the inguinal ligament. In the upper two thirds to three fourths of the abdomen, the aponeurosis passes posterior to the rectus muscle, fusing with the posterior layer of the aponeurosis of the internal oblique muscle, and ends by meeting the one of the opposite side in the linea alba. Insertion occurs also on the xiphoid process at the upper end of the linea alba. In the lower one fourth to one third of the abdomen, the aponeurosis passes anterior to the rectus muscle to reach the linea alba. The lower fibers of the transversus abdominis muscle have a common insertion with the lower fibers of the internal oblique, as described with the insertion of the latter muscle above. The transversus abdominis muscle is often described as having an inferior free border that arches over the spermatic cord in the male (round ligament in the female) from the origin on the external oblique aponeurosis to the pubic attachment. The nerve supply of the transversus muscle comes from the anterior rami of the lower five or six intercostal and subcostal nerves as well as the iliohypogastric, ilioinguinal, and genitofemoral nerves. The actions of the transversus muscle are the same as those listed as being common to the external oblique and other large muscles of the abdomen. Unilateral contraction of one side of the transversus abdominis muscle will not produce appreciable rotation.

The *rectus abdominis* is a flat, vertical muscle, located just lateral to the anterior midline, which is wider and thinner superiorly and becomes narrower and thicker



inferiorly. It has a superior and an inferior attachment, each of which is called the origin of the muscle by some authors and the insertion by others. Several incomplete, zigzag, transversely running *tendinous bands* are present in the muscle, creating its distinctive appearance. These are better developed on the anterior surface of the muscle and are closely attached to the anterior wall of the rectus sheath. The one at the level of the umbilicus is segmentally related to the 10th rib. Two are usually

present between the umbilicus and the xiphoid process, and, in about one third of the instances, one is found below the level of the umbilicus. The superior attachment of the rectus muscle is to the anterior surfaces of the fifth, sixth, and seventh costal cartilages, the xiphoid process, and the costoxiphoid ligament. These attachments fall more or less in a horizontal line. The inferior (caudal) or pubic attachment of the rectus muscle is by a short tendon, a broader lateral portion of which ends

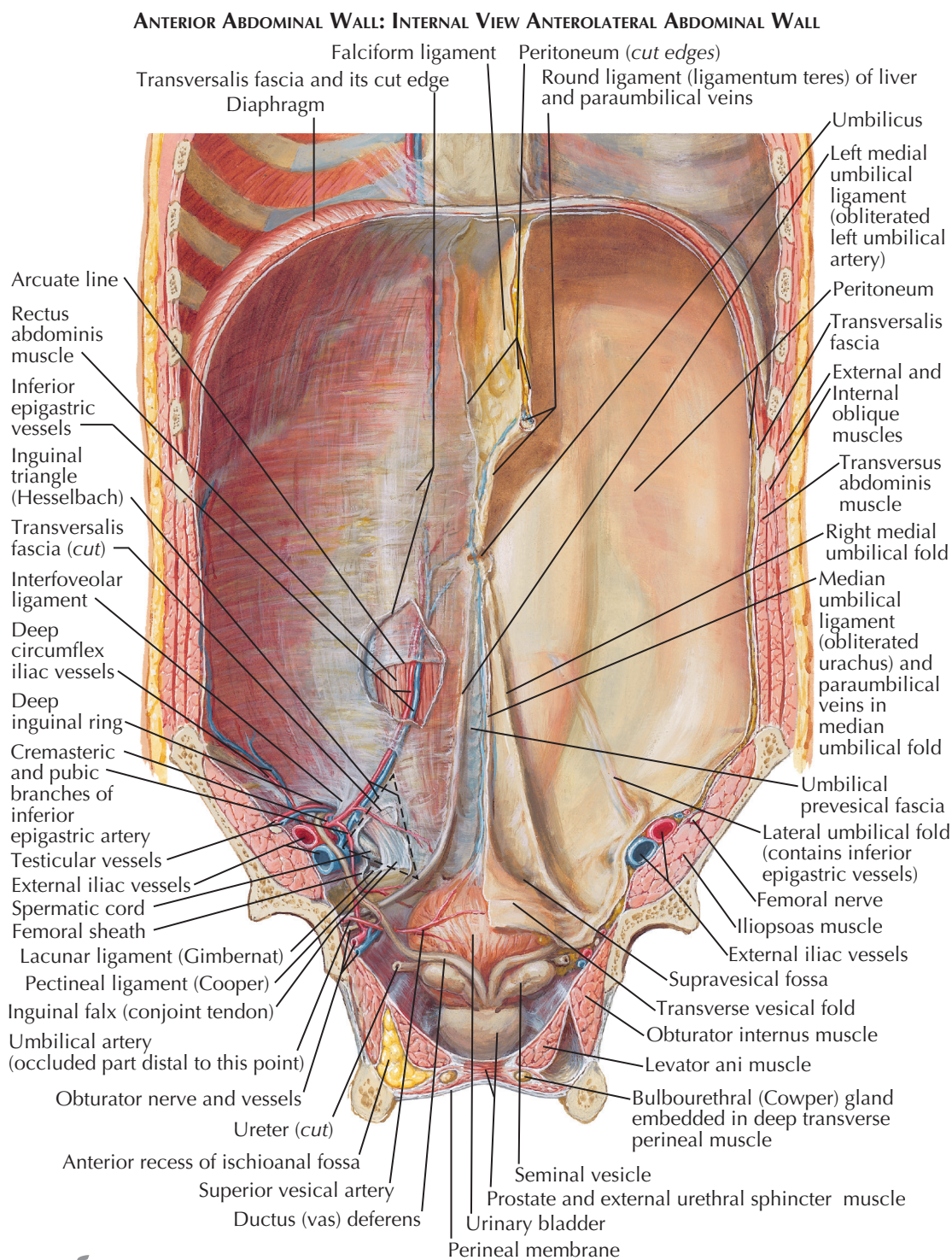
ANTEROLATERAL ABDOMINAL WALL (Continued)

on a roughened area on the pubic crest, extending from the pubic tubercle to the pubic symphysis. The narrower medial portion of the tendon is attached to the front of the symphysis, where it interdigitates with the one of the opposite side. The nerve supply of the rectus abdominis muscle comes from the anterior branches of the anterior rami of the lower six or seven intercostal nerves that enter the deep surface of the muscle near its lateral edge to send cutaneous branches obliquely through the muscle as muscular branches enter into the formation of an intramuscular plexus. The branch from the 10th thoracic nerve usually enters the muscle below the tendinous inscription at the level of the umbilicus. The rectus abdominis muscle generally acts in conjunction with the previously described muscles to compress the abdominal organs and during respiratory expiration. However, it is particularly involved in producing flexion of the vertebral column, bringing the xiphoid and pubic bones closer together.

The *pyramidalis* is a small and seemingly unimportant muscle that is absent in 20% to 25% of the population. It arises from the crest of the pubis, just anterior to the line of attachment of the rectus muscle, and its fibers run superiorly and toward the linea alba, into which they insert as high as one third of the distance to the umbilicus. The *pyramidalis* is supplied by a branch from the subcostal nerve and, sometimes, also the iliohypogastric or ilioinguinal nerves. No biomechanical importance is ascribed to this muscle, although it does tense the linea alba, anchoring it to the pubic bones.

The rectus abdominis and *pyramidalis* muscles are wrapped in a sheath formed, for the most part, by the aponeuroses of the three large flat muscles of the anterolateral abdominal wall, the make-up of which differs in the lower one fourth to one third of the abdomen from the make-up of the rest of its length. In the upper two thirds to three fourths of the abdomen, the aponeurosis of the external abdominal oblique muscle fuses with the anterior lamella of the aponeurosis of the internal abdominal oblique muscle to form the anterior layer of the rectus sheath, and the aponeurosis of the transversus abdominis muscle fuses with the posterior lamella of the internal oblique aponeurosis to form the posterior layer of the rectus sheath. The anterior and posterior layers of the sheath fuse medial to the rectus muscle in the linea alba, and, at the lateral margin of the rectus muscle, the anterior and posterior layers come together at the line of the splitting of the aponeurosis of the internal oblique. The posterior layer of the sheath does not extend superior to the costal margin, so that the uppermost part of the rectus muscle lies directly on the chest wall. In the lower part of the abdomen, the aponeurosis of the internal oblique muscle does not split into two layers, and both it and the greater part of the aponeurosis of the transversus muscle pass anterior to the rectus muscle, so that only the *transversalis fascia* forms the *posterior layer of the rectus sheath* in this area. Usually, the inferior margin of the definitely aponeurotic part of the posterior layer of the sheath is an obvious margin, called the *arcuate line*.

The transversalis fascia is thin and adherent in some areas and thickened and more independent in others. At the arched lower border of the transversus muscle,



the transversalis fascia is thought to fuse with the fascia on the external surface of the transversus and to form a sheet extending to the inguinal ligament. This fascia extends deep to the inguinal ligament to form the anterior wall of the femoral sheath. Lateral to this, in the area where the transversus abdominis arises from the turned-under edge of the external oblique aponeurosis and the related iliac fascia, the transversalis fascia fuses with the iliac fascia.

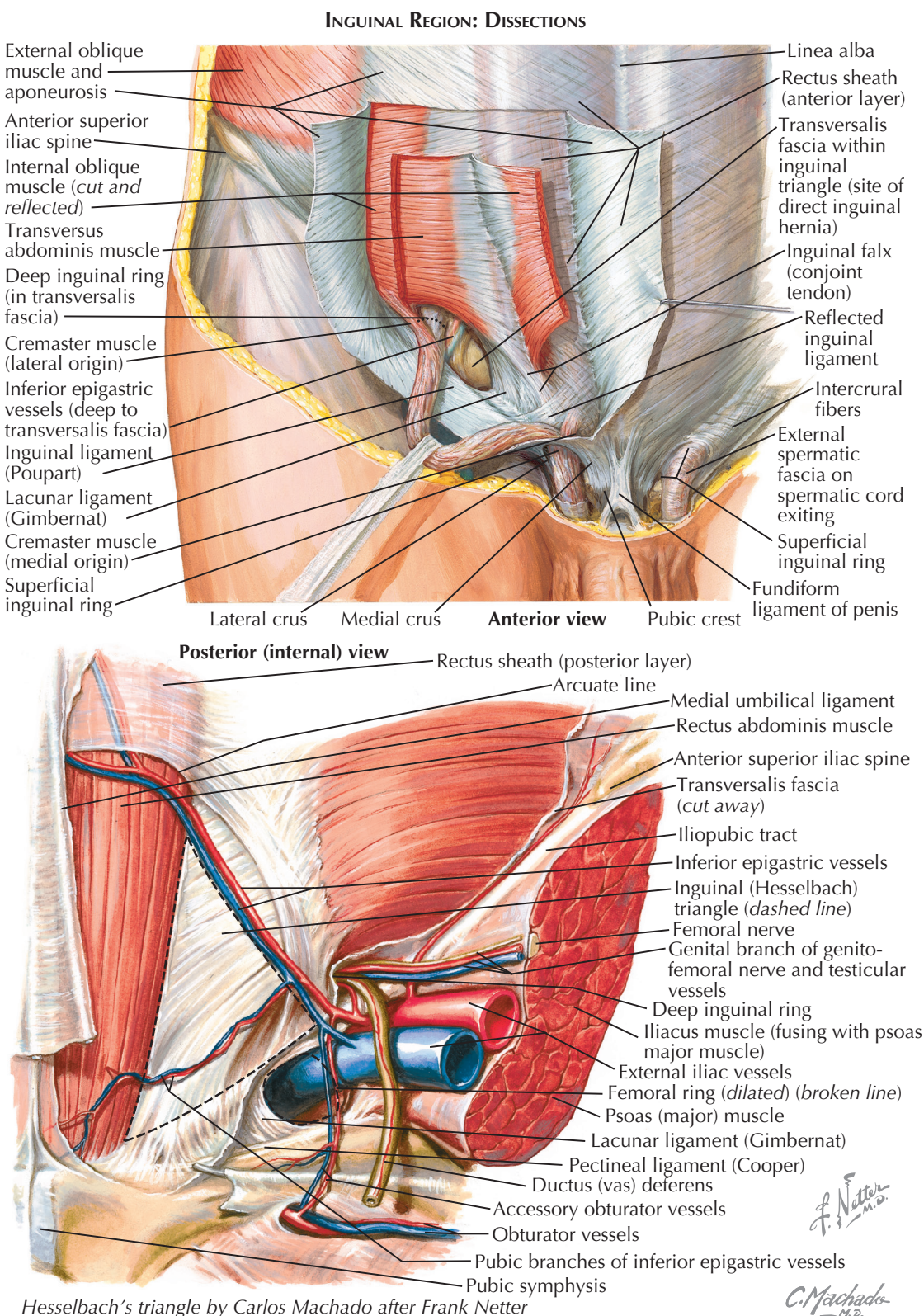
The extraperitoneal fascia (subserous fascia) is thin and comparatively free from fat on the roof and anterolateral abdominal wall, except in the lowest portion, where it is loose and fatty to allow for the expansion of the bladder. In contrast to the situation on the roof and most of the anterolateral abdominal wall, the extraperitoneal tissue on the posterior wall of the abdominal cavity is large and quite fatty, particularly around the great vessels and kidneys.

INGUINAL CANAL

The space occupied by the spermatic cord and its coverings as it passes obliquely through the anterolateral abdominal wall in the male is called the inguinal canal. A similar inguinal canal is present in the female; it transmits the round ligament of the uterus toward its termination in the labia majora. For the sake of convenience, the description given here will be based on the male. In general, it can be said that the canal and the structures described in relation to it are much the same in the female, although somewhat narrower.

The inguinal canal is an oblique tunnel, 3 to 5 cm long, through the muscular and deep fascial layers of the anterior abdominal wall that lie parallel to and just above the *inguinal ligament*. The canal extends between the *deep inguinal ring*, located in the *transversalis fascia* approximately halfway between the *anterior superior spine of the ilium* and the *pubic symphysis*, and the *superficial inguinal ring*, located in the *aponeurosis of the external abdominal oblique muscle* just superior and lateral to the pubic tubercle. The *deep inguinal ring* can be described as a funnel-shaped opening in the transversalis fascia, because it is the site at which this fascia is continued onto the spermatic cord to become the innermost covering of the cord, the *internal spermatic fascia*. The *inferior epigastric vessels* are just inferomedial to the deep inguinal ring, and the most lateral part of the inferior border of the transversus muscle is just superolateral to this ring. The superficial inguinal ring is formed by a splitting apart of the fibers of the external abdominal oblique aponeurosis, with those fibers that pass superomedial to the ring going to intermingle with similar ones of the opposite side and attach to the anteroinferior surface of the symphysis pubis. This portion of the external oblique aponeurosis is called the *medial crus of the superficial ring*. The fibers of the external oblique aponeurosis that pass inferolateral to the superficial inguinal ring are the *lateral crus of the ring*, which, in a sense, is the medial end of the inguinal ligament.

The lower border of the external abdominal oblique aponeurosis is folded under upon itself, with the edge of the fold (and variable added fibrous strands) forming the inguinal ligament. The fascia lata on the anterior aspect of the thigh is closely blended to the full length of the inguinal ligament. Its lateral half, folded deep to the aponeurosis, is firmly fused with the iliac fascia as the iliacus muscle passes into the thigh. As to the medial half of the inguinal ligament, the folded edge is actually formed by the fibers of the aponeurosis rolling under in such a way that the fibers forming the inferolateral margin of the superficial inguinal ring become the most inferior fibers at the attachment to the pubic bone and thus attach most inferiorly on the pubic tubercle, whereas the fibers that were originally more inferior attach higher up on the tubercle and in sequence along the medial part of the pecten pubis for a variable distance, with the lowest fibers in the aponeurosis attaching farthest laterally on the pecten. The portion of the aponeurosis that runs posteriorly and superiorly from the folded edge to the pecten pubis can be called the pectineal part of the inguinal ligament, or the *lacunar ligament*. The fibers of the external oblique aponeurosis, described above, are attached to the pubic tubercle and the pecten pubis and continue, to a varying extent,



beyond these points of attachment. Those which continue from the pecten pubis superiorly and medially superficial to the *conjoined tendon* reach the midline and blend somewhat with the external oblique aponeurosis of the opposite side. They are called the *reflected inguinal ligament*.

Lateral to the superficial inguinal ring, variable fibrous strands course roughly perpendicular to the fibers of the external oblique aponeurosis and are blended with the fibers of the superficial surface of this

aponeurosis. These fibers, called the *intercrural fibers*, can be thought of as helping to prevent the split between the two crura of the external oblique aponeurosis (the superficial inguinal ring) from extending farther laterally.

Another structure that is frequently described as being formed by fibers from the external abdominal oblique aponeurosis, and which has considerable clinical significance as a firm structure to which sutures can be anchored in the surgical repair of hernia, is the

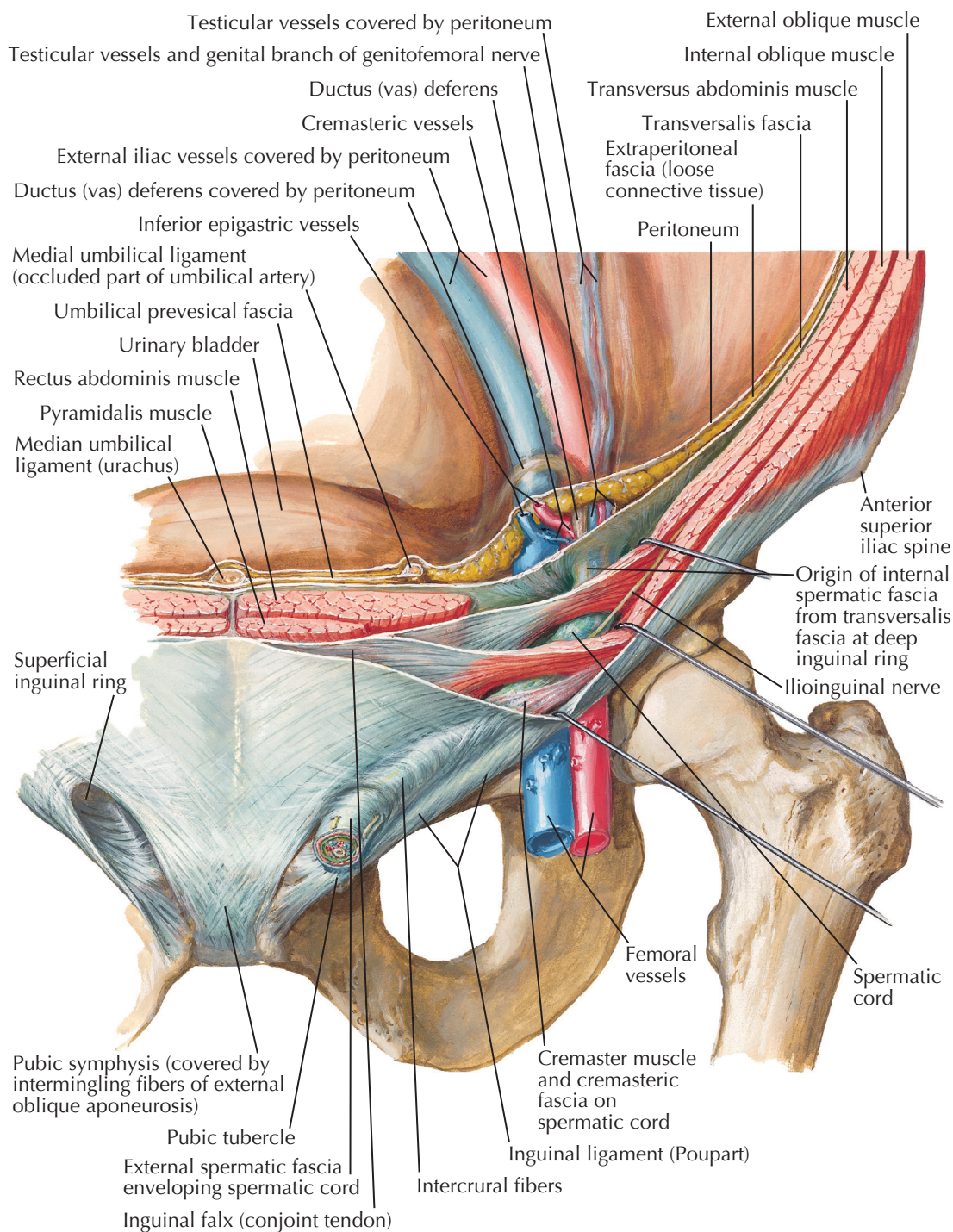
INGUINAL CANAL AND SPERMATIC CORD

INGUINAL CANAL (Continued)

pectineal ligament (Cooper ligament). This ligament runs along the sharp edge of the pecten pubis and has the effect of heightening this ridge. It is often described as being formed by fibers of the lateral part of the pectineal portion of the inguinal ligament (lacunar ligament) which, as they approach the pecten, turn sharply superolaterally to run along it. The pectineal ligament can also be interpreted as a building up of the periosteum along the pecten pubis, which is more in keeping with what appears to be the situation in many cadavers.

The origins and insertions of the internal abdominal oblique muscle and the transversus abdominis muscle have been described previously, but certain details in regard to the portions of these muscles related to the inguinal canal merit additional description. The exact amount of the turned-under edge of the external abdominal oblique aponeurosis (and the adjacent iliac fascia to which this edge of the aponeurosis is closely related) from which these two muscles take origin is quite variable, and it may be difficult to separate muscles in this area. The origin of the internal oblique muscle, more times than not, extends far enough medially so that some fasciculi of the muscle are anterior to the spermatic cord as its constituent structures come together at the deep inguinal ring, thus reinforcing this area to a certain extent. The origin of the transversus abdominis muscle (if it can be adequately separated) usually does not extend medially beyond the lateral border of the superficial inguinal ring, if it extends even that far. Because the conjoined tendon inserts on the pecten pubis and the crest of the pubis and thus along a line that angles from the pecten onto the crest, the part of this tendon inserting on the pecten is in one plane and that inserting on the crest is in a somewhat different plane. The part of the conjoined tendon inserting on the pecten pubis is partially fitted to the contour of the spermatic cord, and it approaches the pecten from posterior to the spermatic cord to meet the lacunar ligament (pectineal part of the inguinal ligament), which approaches the pecten from below the spermatic cord.

The inguinal canal and the structures within it can be further elucidated by thinking of this tubular tunnel as having a roof, a floor, and anterior and posterior walls, although, of course, because the tunnel is shaped to accommodate a cylindrical structure (the spermatic cord), no sharp boundary between any of the four walls can be established. It should be further remembered that the openings at the ends of the tunnel are not in planes perpendicular to the long axis of the tunnel but are in planes that form an acute angle with the long axis of the tunnel, so that the posterior wall of the canal extends farther medially than does the anterior wall and the anterior wall extends farther laterally than does the



posterior wall. The two openings, of course, are the deep inguinal ring in the transversalis fascia at the internal end of the canal and the superficial inguinal ring in the aponeurosis of the external abdominal oblique muscle at the external end of the canal. The external abdominal oblique aponeurosis, strengthened by the *intercrural fibers*, is present in the entire length of the anterior wall of the canal. For approximately the lateral one quarter to one third of the canal, fibers of the internal oblique muscle, which arise from the inguinal

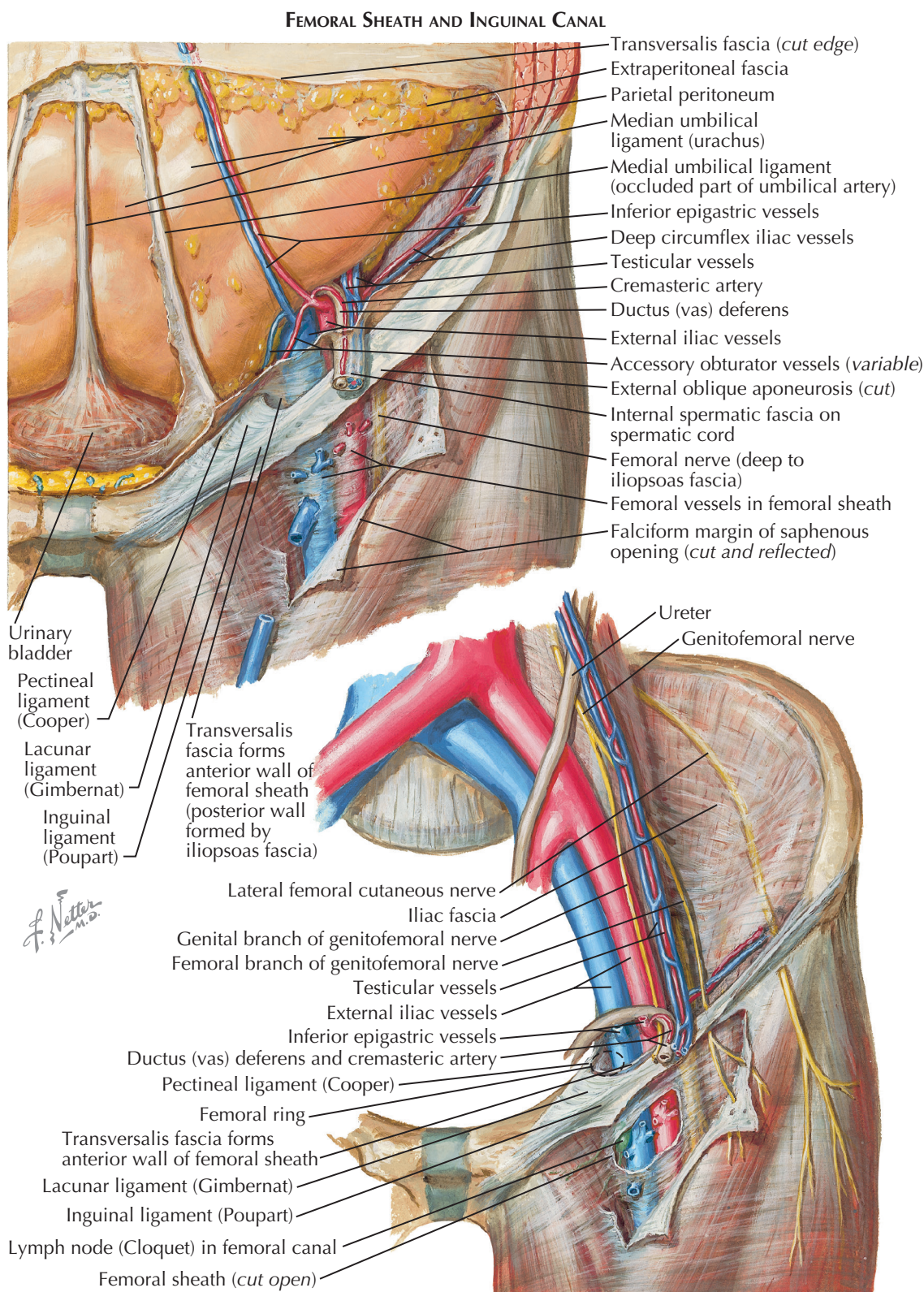
ligament and related iliac fascia, form the anterior wall of the canal deep to the external oblique aponeurosis. Superficial to the external oblique aponeurosis lie the superficial fascia and the skin, which continue medially beyond the anterior wall of the canal above the superficial inguinal ring. The *floor (inferior boundary) of the canal* is formed in its medial two thirds to three quarters by the rolled-under portion of the external oblique aponeurosis together with the lacunar ligament (pectineal portion of the inguinal ligament), forming a shelf upon

INGUINAL CANAL (Continued)

which the spermatic cord rests. The transversalis fascia is present for the entire length of the *posterior wall of the canal*. Toward the medial end of the canal, and thus reinforcing the part of this wall posterior to the superficial inguinal ring, is the reflected inguinal ligament to the extent present just anterior to the conjoined tendon of the transversus and internal oblique muscles. A quite variable expansion from the tendon of the rectus abdominis muscle (called by some authors the inguinal falx) fuses, to a variable extent, with the posterior aspect of the conjoined tendon. All of the reinforcing structures just described are, of course, anterior to the transversalis fascia. Posterior or deep to the transversalis fascia are the loose extraperitoneal fascia and *peritoneum*, which continue across posterior to the deep inguinal ring. At the lateral end of the canal, the *inferior epigastric artery and vein* are posterior to the canal in the extraperitoneal fascia as they are in relation to the medial (inferomedial) margin of the deep inguinal ring. Overlying these vessels, a thickening in the transversalis fascia is variably present. A slight depression in the parietal peritoneum, as seen from within, is apt to be present at the site of the deep inguinal ring. The *roof of the inguinal canal* can be said to be formed by the most inferior fasciculi of the internal oblique muscle as they gradually pass in a slightly arched fashion, from a position at their origin anterior to the canal to a position at their insertion (by way of the conjoined tendon) posterior to the canal. At the lateral end of the canal, the lower fasciculi of the transversus abdominis arch similarly over the canal. It should be pointed out that, although the description above of a roof and a floor of the canal can serve a useful purpose in talking about the canal, the anterior and posterior walls of the canal, in a sense, come together superior and inferior to the canal, and the roof and much of the floor are, perhaps, manufactured for descriptive purposes.

The weakest area in the anterolateral wall in relation to the inguinal canal is the superficial inguinal ring, which, to a varying extent, is reinforced by the reflected inguinal ligament, the conjoint tendon, and the expansion laterally and inferiorly from the tendon of the rectus abdominis muscle to the pecten pubis. This generally weakened area, the inguinal (Hesselbach) triangle, through which a direct inguinal hernia will pass, is a triangle bounded superolaterally by the inferior epigastric vessels, superomedially by the lateral margin of the rectus, and inferiorly by the inguinal ligament.

Developmentally, the inguinal canal is established as an outpouching in the inferior part of the anterior abdominal wall, the *processus vaginalis*, containing all of the layers from the parietal peritoneum outward, in preparation for the descent of the testes from their origin along the posterior abdominal wall through the



inguinal canal and into the scrotum. Originally, the process was straight in an anterior-posterior direction, but further regional development causes it to become oblique. The processus vaginalis normally loses its connection with the parietal peritoneum of the abdominal cavity, and all that remains of this is the double-walled serous sac, the *tunica vaginalis*, that partially surrounds the testis. The outpouchings of the other layers remain as coverings of the spermatic cord and testis which are picked up by the spermatic cord as

it passes through the successive layers of the anterolateral abdominal wall. The covering acquired from the transversalis fascia is called the *internal spermatic fascia*. The spermatic cord is typically described as having passed inferior to the lower border of the transversus abdominis. The covering derived from the internal abdominal oblique muscle is the *cremasteric muscle and fascia*. The covering of the spermatic cord and testis procured from the external abdominal oblique muscle is the *external spermatic and intercrural fasciae*.

POSTERIOR WALL OF ABDOMINAL CAVITY

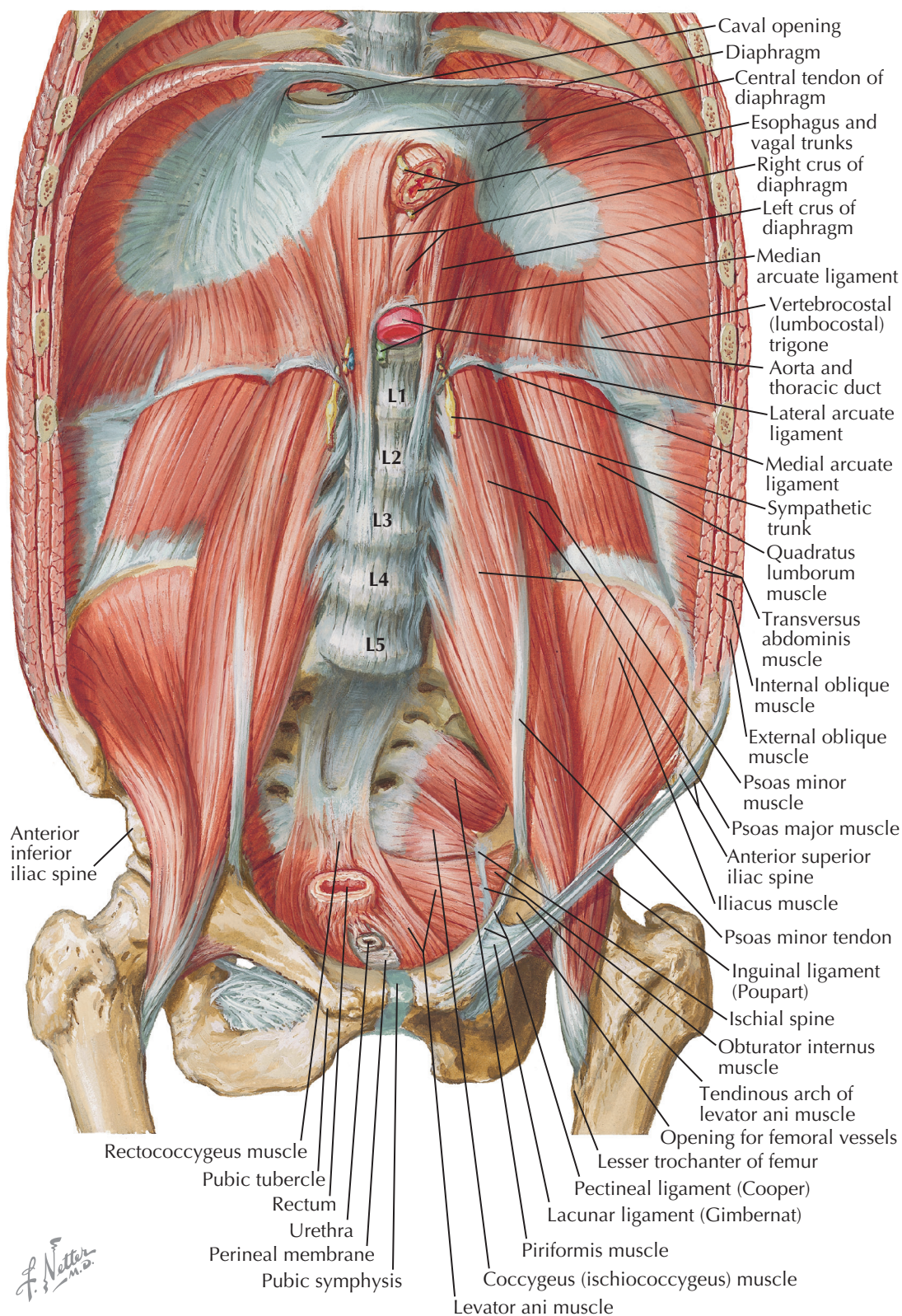
The bodies of the five *lumbar vertebrae*, together with the related *intervertebral discs*, form a distinct, longitudinal, midline elevation in the posterior wall of the abdominal cavity, which may actually come within a relatively short distance (a few centimeters) of the inner surface of the anterior abdominal wall. The intervertebral disks produce bulges in this elevation, and the *anterior longitudinal ligament*, with the closely attached crura of the diaphragm, covers its anterior surface. Just lateral to the lumbar vertebrae are the *psaos major* and *minor muscles* (if present). Lateral to the *psaos major* muscle in the area inferior to the crest of the ilium is the *iliacus muscle*, and in the area between the 12th rib and the crest of the ilium is the *quadratus lumborum muscle*.

The *psaos major muscle* arises from (1) the anterior surfaces of the bases and the inferior borders of the transverse processes of all of the lumbar vertebrae; (2) the lateral aspect of the intervertebral disc above each of the lumbar vertebrae and from the adjacent parts of the vertebra above and the vertebra below each of these discs; and (3) from tendinous arches stretching across the concavity at the side of the body of each of the first four lumbar vertebrae. This muscle courses inferiorly along the brim of the pelvis and passes inferior to the inguinal ligament to enter the thigh and insert on the lesser trochanter of the femur.

Present in 40% to 60% of the cases, the *psaos minor muscle* arises from the lateral aspect of the bodies of the 12th thoracic and 1st lumbar vertebrae and the intervertebral disc between them. It courses inferiorly on the anterior aspect of the *psaos major*, ending in a long flat tendon that inserts into the pecten pubis and the iliopectineal eminence.

The *iliacus muscle* fills much of the iliac fossa (which actually forms the lateral wall of this part of the abdominopelvic cavity) and arises from the upper two thirds of this fossa, the inner lip of the crest of the ilium, the anterior sacroiliac and iliolumbar ligaments, and the base of the sacrum. Its fibers converge as they course inferiorly to insert, for the most part, into the lateral side of the tendon of the *psaos major* muscle. Some of the fibers also insert onto the femur just inferior and anterior to the lesser trochanter. Because most of the *iliacus muscle* inserts into the tendon of the *psaos major*, the two muscles are often described as the *iliopsoas muscle* and, of course, have a common action.

The *quadratus lumborum muscle* arises from the posterior part of the iliac crest (inner lip), the iliolumbar ligament, and the transverse process of the 5th lumbar vertebra (and perhaps 4th, 3rd, and 2nd lumbar vertebrae for a sometimes-demonstrable anterior layer of the muscle), and inserts into the lower border of the medial part (half or so) of the 12th rib, with some insertion



into the transverse processes of the upper four lumbar vertebrae. It draws the last rib inferiorly and thus acts as anchorage for the diaphragm to the crest of the ilium, and it also bends the lumbar portion of the lumbar spine laterally. Its anterior surface is covered by a variably thin, anterior layer of the thoracolumbar fascia. Its posterior side is in contact with the thoracolumbar fascia's middle layer.

The posteroinferior part of the diaphragm may be considered as part of the posterior abdominal wall.

Depending on where the posterior limit of the antero-lateral abdominal wall is arbitrarily located, the portions of the transversus abdominis muscle (overlain by the internal and external oblique muscles) just lateral to the quadratus lumborum muscle can also be considered as helping to form the posterior abdominal wall.

The superficial structures of the lower part of the back are, of course, external to what has been described here and would have to be traversed were the abdominal cavity approached from behind.

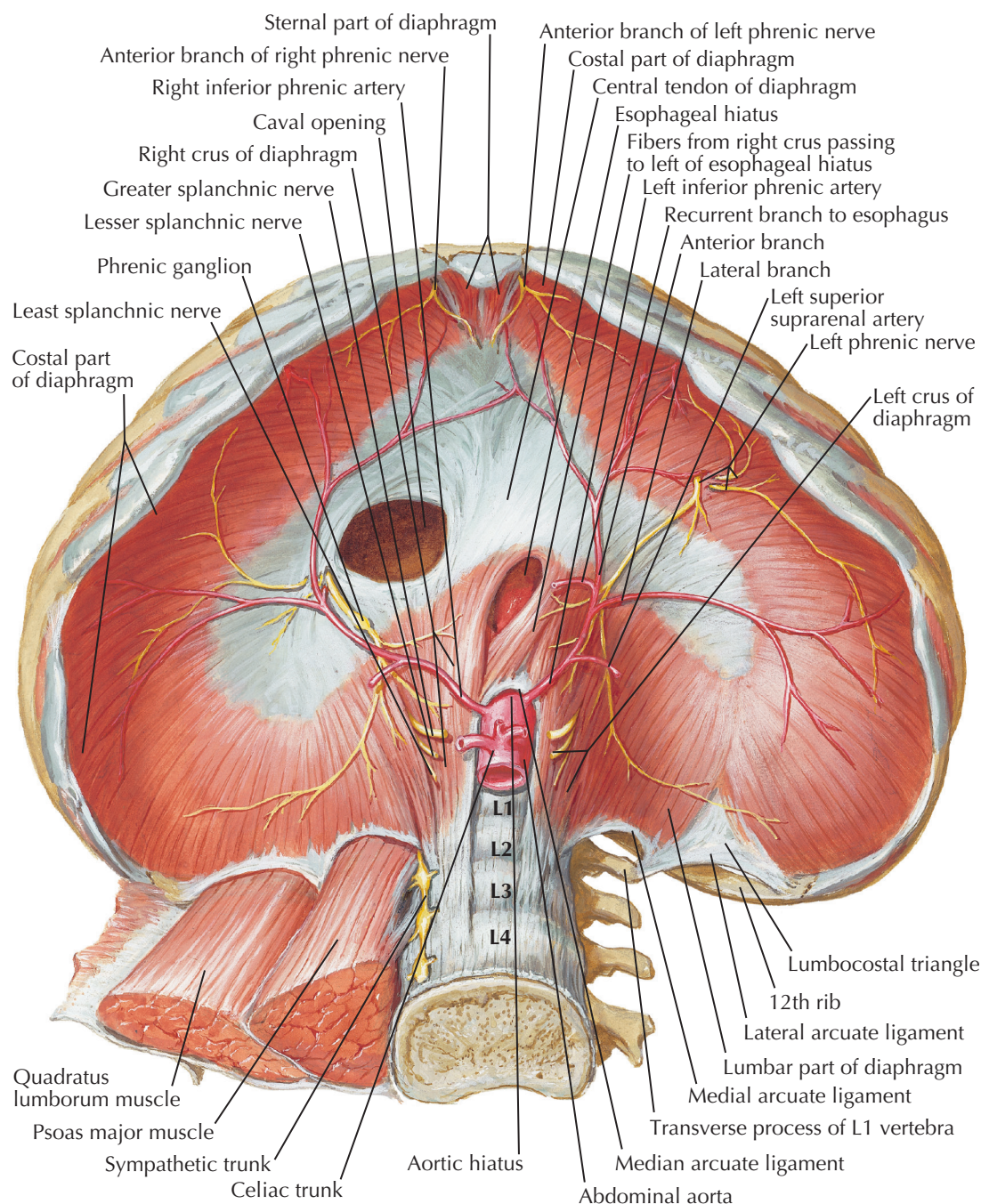
DIAPHRAGM

The dome-shaped roof of the abdominopelvic cavity is formed by a musculoaponeurotic septum, the diaphragm, which also forms the floor of the thoracic cavity and thus is the partition between these two cavities. This unique muscular structure takes origin by its entire circumference from the inner aspect of the *lower margin of the thoracic cage*. The muscular fibers course superiorly and inward to insert in the margins of the diaphragm's *central tendon*. The sternal origin is, by way of a fairly short, fleshy slip (a right and a left one), on the posterior aspect of the xiphoid process, which, on its way to the anterior margin of the central tendon, does not ascend nearly as much as do the fibers from the other two areas of origin. In fact, depending on the position of the individual and the degree of contraction of the diaphragm, the fibers from the sternal origin may even course inferiorly.

The costal origin in general arises from the inner surfaces of the costal cartilages and the adjacent parts of the lower six ribs by fibers from each that interdigitate with the origin of the transversus abdominis muscle. The lumbar origin consists of a *crus* and a *medial arcuate ligament* and a *lateral arcuate ligament* on each side. The crura begin as tendinous structures, which attach to the anterior and lateral sides of the upper lumbar vertebrae (one to three or four for the right and one to two or three for the left) and related intervertebral disks, blending with the anterior longitudinal ligament. The *right crus* is stouter as well as longer than the left and, as it becomes muscular, usually splits to send a portion to the left of the *esophageal hiatus*. The medial margins of the two crura converge to meet in the midline to form an arch across the anterior aspect of the aorta, the *median arcuate ligament*. The medial arcuate ligament is a tendinous arch that appears as a thickening in the fascia over the superior part of the *psoas major muscle*, extending from the side of the body of the second (or first) lumbar vertebra, where it blends with the lateral margin of the corresponding crus to the end of the *transverse process* of the first (or second) *lumbar vertebra*. The lateral arcuate ligament is a thickening in the fascia that covers the *quadratus lumborum muscle* and reaches from the end of the transverse process of the 1st (or 2nd) lumbar vertebra to the tip and lower margin of the 12th (or 11th) rib.

The central tendon is a thin but strong and dense aponeurosis, closer to the sternal origin than the costal and lumbar origins. It is shaped somewhat like a thick and widely opened V, with slight indentations, which produce three leaflets. The fibrous pericardium is blended with its superior surface.

Several openings (hiatuses) permit the passage of structures between the thoracic and abdominal cavities.



The inferior vena cava passes through the *caval opening* at the junction of the right and middle leaflets of the central tendon in the most anterior and highest of the three large openings, being at the level of the disc between T8 and T9. It often transmits a branch of the phrenic nerve. The *esophageal hiatus* is in the muscular portion of the diaphragm just posterior to the central tendon, a little to the left of the midline and about at the level of T10, and transmits the esophagus as well as the anterior and posterior vagal trunks to the abdomen.

The *aortic hiatus* (really a notch in the posterior margin of the diaphragm) is at the level of T12 and transmits the thoracic duct and *azygos vein* in addition to the aorta. The *greater and lesser splanchnic nerves* pierce the crura, and, in addition, the left crus is pierced by the *hemiazygos vein*.

Intervals at the origin where muscle is replaced by areolar connective tissue occur at the sternocostal triangle and, with great variation, at the lateral arcuate ligaments.

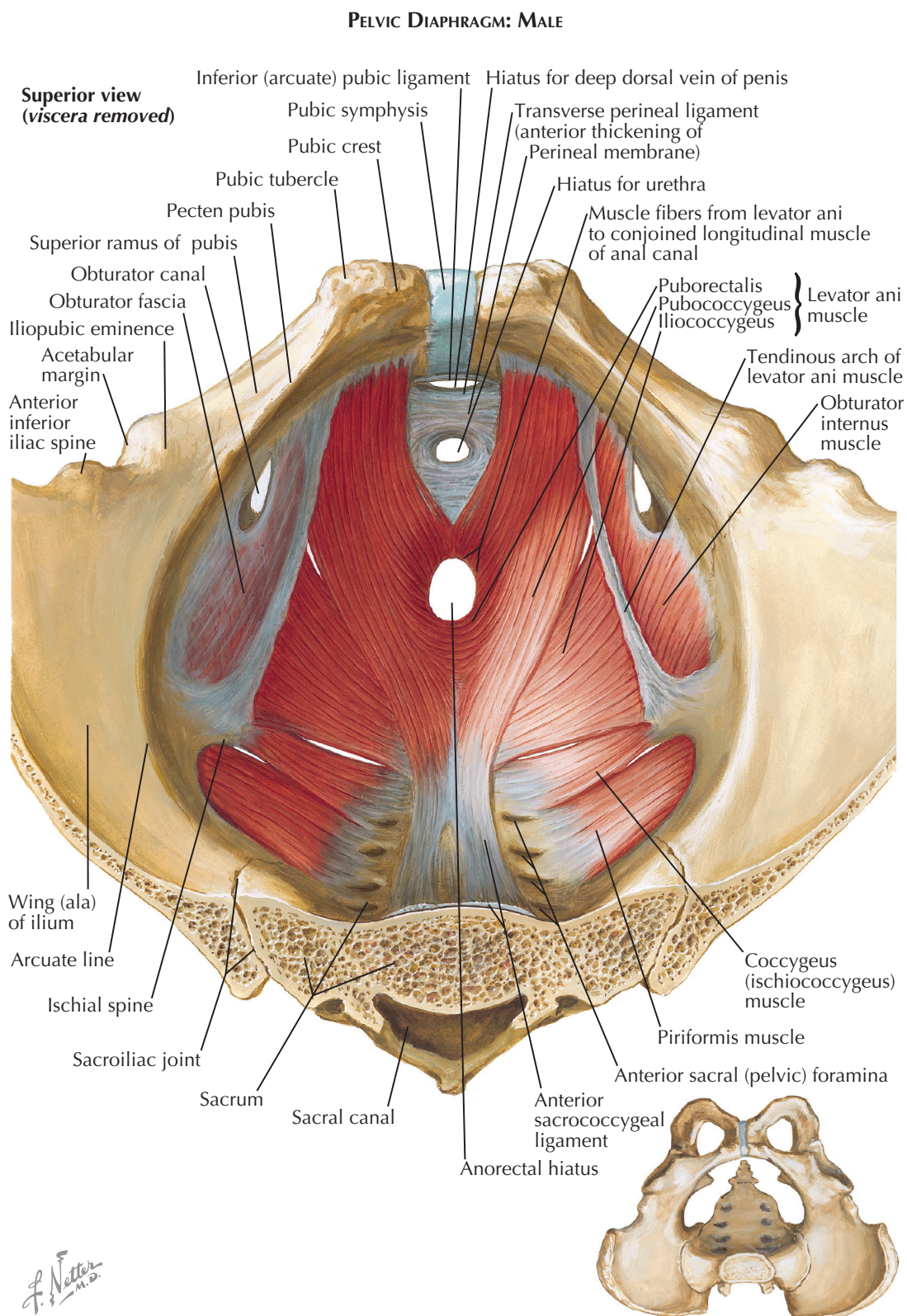
FLOOR OF ABDOMINOPELVIC CAVITY

The outlet of the pelvis (inferior aperture of the pelvis) is, for the most part, closed by the slinglike structure known as the pelvic diaphragm that, together with the urogenital diaphragm, gives the inferior and posteroinferior support to the abdominopelvic viscera. As usually described, the pelvic diaphragm consists of the right and left levator ani muscles, the right and left coccygeus muscles, and the fascia on both surfaces of these muscles.

The *levator ani* muscle arises (1) from the pelvic surface of the pubis along a line from a little lateral to the inferior part of the pubic symphysis toward the *obturator foramen*, (2) from the *tendinous arch of the levator ani*, which is a thickening of the fascia on the pelvic surface of the *obturator internus* muscle along a line extending from the lateral end of the pubic origin of the levator ani to the *ischial spine*, and (3) from the pelvic surface of the *ischial spine*. In general, the fibers of the right and left levator ani muscles run posteriorly, inferiorly, and medially, with varying degrees of obliquity, to come into relationship with each other in the midline by inserting into the perineal body, as well as the anterior and lateral sides of the coccyx, or to blend closely with the midline viscera, interposed between the two muscles. The levator ani can be described in at least three parts: (1) The *puborectalis* muscle, has fibers inserting into the perineal body, clasp the prostate in the male and the vagina in the female. The remaining fibers form a sling around the anorectal junction. (2) The intermediate set of fibers, found lateral and slightly superior to the puborectalis, form the *pubococcygeus* muscle. It originates from the posterior aspect of the pubic bone and the tendinous arch of the levator ani to insert into the coccyx and anococcygeal ligament. (3) The remainder of the levator ani muscle is the *iliococcygeus* muscle, which originates from the tendinous arch of the levator ani and inserts onto the lateral aspect of the coccyx. The nerve supply of the levator ani muscle is from the fourth sacral nerve by way of the perineal branch of the pudendal nerve.

The *coccygeus* muscle, which is closely applied to the deep surface of the sacrospinous ligament and is in much the same plane as the iliococcygeus muscle, is a flat triangular muscle arising from the ischial spine and inserting into the margin of the lower two sacral segments and the first two segments of the coccyx. It receives its nerve supply from the anterior primary ramus of the fourth sacral nerve.

The bony framework of the true pelvis (pelvis minor), supplemented by the sacrospinous and sacrotuberous



ligaments, presents several openings, each of which is, to a great extent, closed by muscle. The *obturator internus*, a muscle of the lower extremity, covers the obturator foramen except for the much smaller obturator canal through which the obturator vessels and nerve pass. It arises from the pelvic aspect of the *obturator fascia* and the adjacent bone and passes through the lesser sciatic foramen (mostly filling this opening) on its way to the medial side of the greater trochanter of

the femur, where it inserts. Anterosuperior to the origin of the levator ani muscle, the obturator internus muscle forms a portion of the wall of the pelvic cavity. The *piriformis*, also a muscle of the lower extremity, arises from the pelvic surface of the sacrum between, and lateral to, the second, third, and fourth anterior *sacral foramina* and mostly fills the greater sciatic foramen in traversing this foramen on its way to insert on the summit of the greater trochanter of the femur.

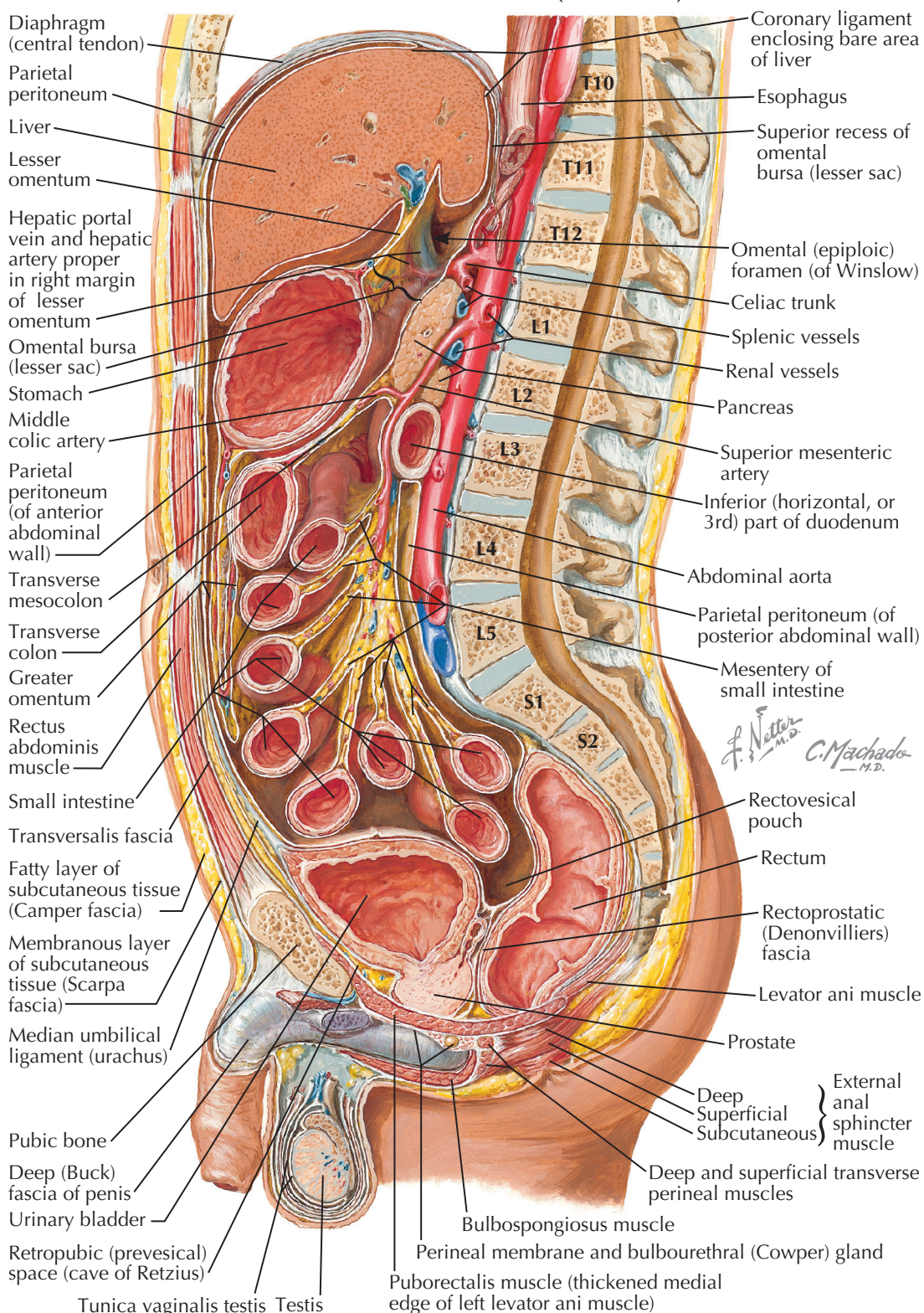
ABDOMINAL WALL AND VISCERA: PARAMEDIAN (PARASAGITTAL) SECTION

PERITONEUM

The peritoneum is the extensive serous membrane that, in general, lines all borders of the abdominopelvic cavity and reflects from the body wall onto the organs that are contained within it. A general concept that one might have of the pleura or the serous pericardium can be carried over to the peritoneum. In all of these situations, the serous membrane lining the body wall is continuous with that on the surfaces of the viscera contained within the portions of the body cavity involved, and although one refers separately to parietal and visceral portions of the serous membrane, they are continuous. Also, under normal circumstances, the organs fill the respective portion of the body cavity so completely that the visceral and parietal portions of adjacent structures are separated from each other by only a thin film of fluid. The peritoneal cavity of the female is the only place where an organ's lumen is in direct contact with the peritoneal space, as the opening of each uterine tube is open to the peritoneal cavity.

The peritoneum is much more complicated in its arrangement than either the visceral pleura or the serous pericardium. This is essentially due to the fact that parts of several viscera deform the peritoneal serous membrane to various degrees in the course of fetal development. The rotations of the gut, combined with the propensity of one free peritoneal surface to fuse with another free surface, result in complex changes of the arrangement that lead to the mature appearance of the abdominal organs. The stomach (to cite only one example of the manifold rearrangements in the visceroperitoneal relations) in its primary vertical position was attached by one double layer of peritoneum, the ventral mesogastrium, to the ventral body wall, and by another double layer, the dorsal mesogastrium, to the posterior wall. When the stomach rotated, its original left side became the anterosuperior surface and the original right side the posteroinferior surface; the dorsal mesogastrium was swept toward the left to form an out-pouching of the peritoneal cavity, which presents itself at an early developmental stage (6 weeks) as the omental bursa (lesser sac), communicating with the rest of the peritoneal cavity (greater sac) by only a small opening, the omental foramen (of Winslow), located a little to the right of the midline posteroinferior to the liver.

The best way to obtain a general concept of the arrangement of the peritoneum is to trace it in three planes, a midsagittal plane and two horizontal planes, one at the level of the pylorus and the other at the level of the umbilicus, in a preferably fresh specimen at the autopsy table. Lacking this opportunity, the use of these three planes still remains methodically the most

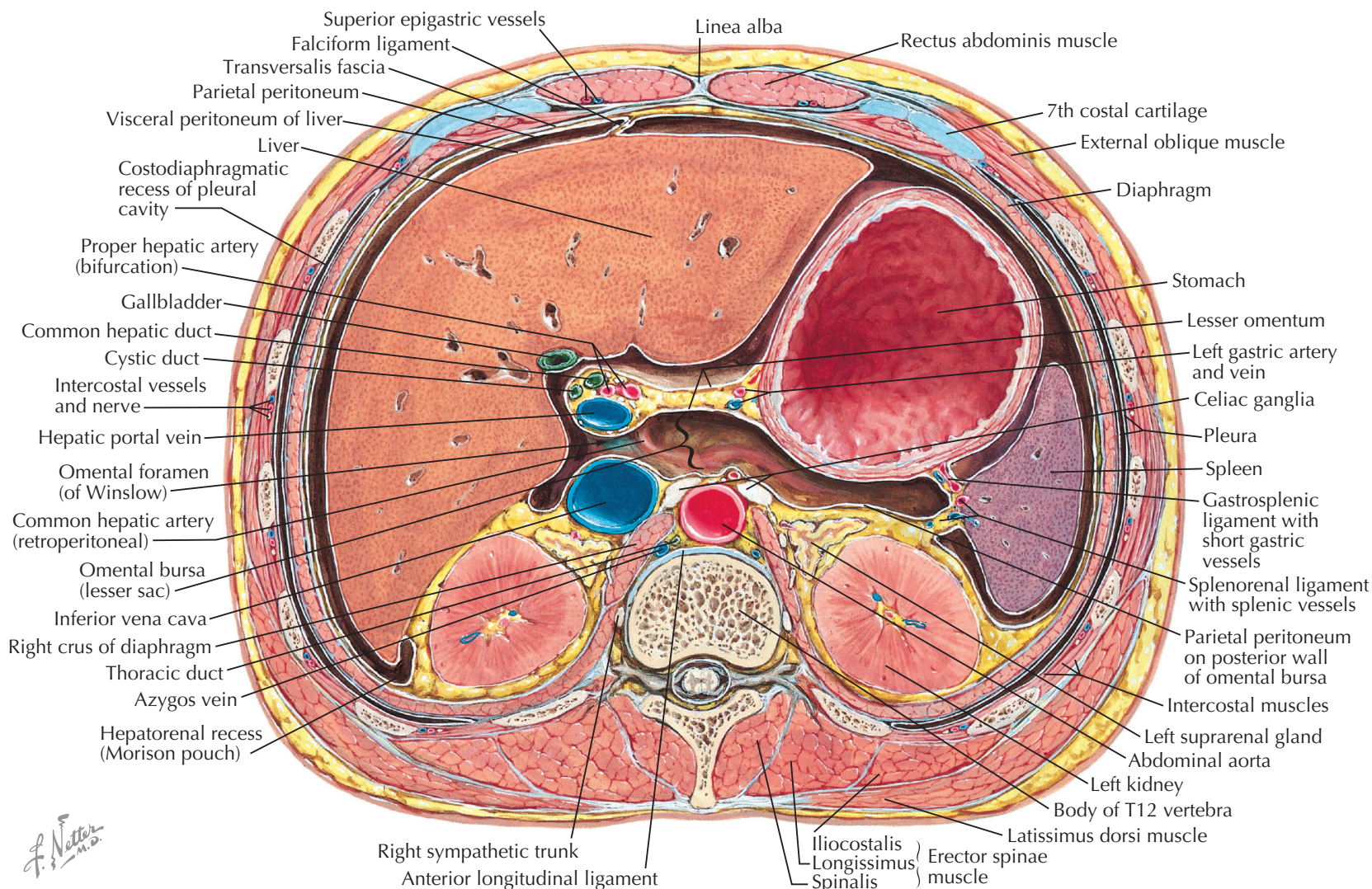


informative approach for studying the peritoneal continuity and its relationship to the abdominopelvic viscera.

In the midsagittal plane, the greater and lesser peritoneal sacs must be pursued separately, because they are not continuous anywhere in this plane. In following the cut edge of the *greater sac*, one can start with the parietal peritoneum on the inner surface of the anterior wall at the level of the umbilicus. Progressing superiorly, the

peritoneum continues onto the inferior surface of the *diaphragm* and along it until it is reflected to the liver as the superior (anterior) layer of the *left triangular ligament*. From here it extends along the anterosuperior surface of the liver, around the free margin of the liver, and onto its visceral surface, until it is reflected toward the lesser curvature of the stomach as the anterior layer of the *lesser omentum*, which then advances onto the anterior surface of the stomach, leaving the latter as the

SCHEMATIC CROSS SECTION OF ABDOMEN AT MIDDLE T12



PERITONEUM (Continued)

anterior surface of the greater omentum. At the free margin of the greater omentum, this layer turns superiorly to become the posterior surface of the greater omentum, which proceeds superiorly to the transverse colon, where it appears to continue onto the posterior surface of the transverse colon and then as the posterior layer of the transverse mesocolon. From the posterior layer of the transverse mesocolon, the peritoneum turns inferiorly from the lower border of the *pancreas* across the anterior surface of the *third portion of the duodenum* and becomes the right (superior) layer of the intestinal mesentery. At its free margin the mesentery entirely (except for the area of mesenteric attachment) surrounds the small intestine and continues to the posterior body wall as the left (inferior) layer of the mesentery. On reaching the body wall, it runs as the *parietal peritoneum of the posterior wall* inferiorly on the anterior surface of the aorta and then on the vertebral column to about the second sacral level, where it comes to lie on the anterior surface of the rectum, from which, in the male, it is reflected onto the posterosuperior surface of the bladder, bounding the *rectovesical pouch*. In the female, the peritoneum passes from the anterior surface

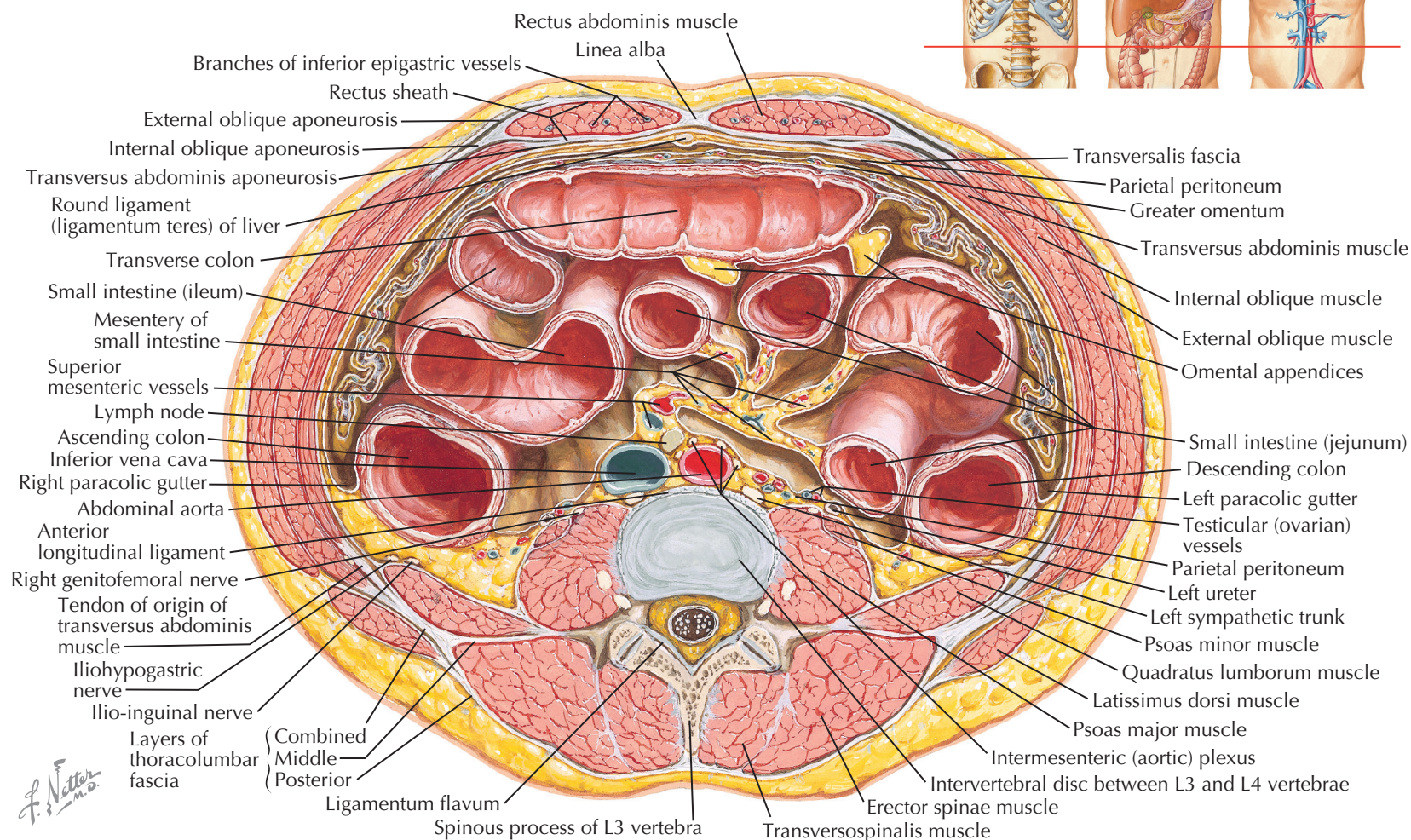
of the rectum to the posterior vaginal fornix, bounding the rectouterine pouch (of Douglas). It passes up the posterosuperior aspect of the uterus, over the fundus of the uterus, and down on its anteroinferior aspect to about the junction of the body and cervix, from whence it reflects onto the posterosuperior aspect of the bladder, bounding the vesicouterine pouch. In both the male and the female, the peritoneum passes from the superior surface of the *bladder* to the inner surface of the anterior body wall, a variable distance above the symphysis pubis, depending on the degree of distention of the bladder. From here it continues superiorly to the point at which this tracing of the peritoneum was started.

In following the cut edge of the omental bursa's peritoneum in a midsagittal plane, a start can be made on the anterior surface of the pancreas, and the peritoneum can be traced superiorly from here onto the surface of the diaphragm until it reflects from the diaphragm to the liver as the inferior (posterior) layer of the left triangular ligament. From here it can be traced along the posterior and then inferior surfaces of the liver to the point at which it leaves the liver to go to the lesser curvature of the stomach as the posterior layer of the lesser omentum, which continues onto the posteroinferior surface of the stomach and to the greater curvature,

where it leaves the stomach to extend for a variable distance into the greater omentum. This distance depends on the degree of fusion of the peritoneum which has taken place, typically not reaching beyond the transverse colon. The peritoneum turns superiorly on the anterior surface of the transverse colon, and then, in the adult, it usually forms the anterior layer of the transverse mesocolon if the fusion of the primitive dorsal mesogastrium with the primitive mesentery of the transverse colon has been complete. The transverse mesocolon comes to the posterior body wall just inferior to the point at which the tracing of the lesser sac peritoneum was started.

In tracing the peritoneum in a horizontal section at the level of the omental foramen, a start can be made with the greater sac peritoneum on the inner surface of the anterior abdominal wall in the midline. Following the cut edge of the parietal peritoneum to the left along the inner surface of the anterolateral wall to the region of the posterior wall, it will pass onto the anterolateral surface of the left *kidney*, from where it reflects to the hilar area of the spleen, forming the external layer of the *splenorenal ligament*, and then completely surrounds the spleen except at the hilar area. From the anterior margin of the hilum of the spleen, the peritoneum passes to the stomach as the external layer of

CROSS SECTION AT L3, 4



PERITONEUM (Continued)

the *gastrosplenic ligament*. The peritoneum can then be followed along the anterosuperior surface of the stomach to the lesser curvature, where it leaves the stomach as the anterior layer of the *lesser omentum*, which can be followed to the right until the free margin is reached a short distance to the right of the midline. Here the peritoneum passes around the free margin of the lesser omentum (anterior boundary of the omental foramen) to become the peritoneum of the omental bursa, which continues to the left, as the posterior layer of the lesser omentum, to the lesser curvature of the stomach, where it continues onto the posteroinferior surface of the stomach, which it follows until it leaves the stomach to form the internal (lesser sac) layer of the *gastrosplenic ligament*. From the spleen the peritoneum forms the internal layer of the *splenorenal ligament* and then travels to the right anterior to the *aorta* and the *inferior vena cava*. At the right margin of the inferior vena cava, the peritoneum again becomes continuous with the greater sac and continues to the right onto the anterior aspect of the right kidney. From here the tracing of the peritoneum could differ, depending on whether the bare area of the liver were to extend

down just far enough to be encountered in the plane of the tracing or whether the plane of tracing passes just inferior to the bare area of the liver. In the former case, the peritoneum would pass from the kidney as the inferior layer of the coronary ligament to the liver, and would follow around the liver to its anterosuperior surface, where it would leave the liver as the left layer of the *falciform ligament*, to go to the inner surface of the anterior body wall and to the left to the point from which the tracing started. To complete the tracing in this plane, one must follow the peritoneum from the right layer of the falciform ligament onto the anterosuperior surface of the liver, and to the right along this surface to the superior layer of the coronary ligament, along this to the diaphragm, and then anteriorly to the right layer of the falciform ligament. If the plane of section passes just inferior to the bare area of the liver as the peritoneum leaves the anterior surface of the inferior vena cava (the posterior boundary of the omental foramen), it passes across the anterior surface of the right kidney, then to the diaphragm, and forward on the inner surface of the body wall to the falciform ligament.

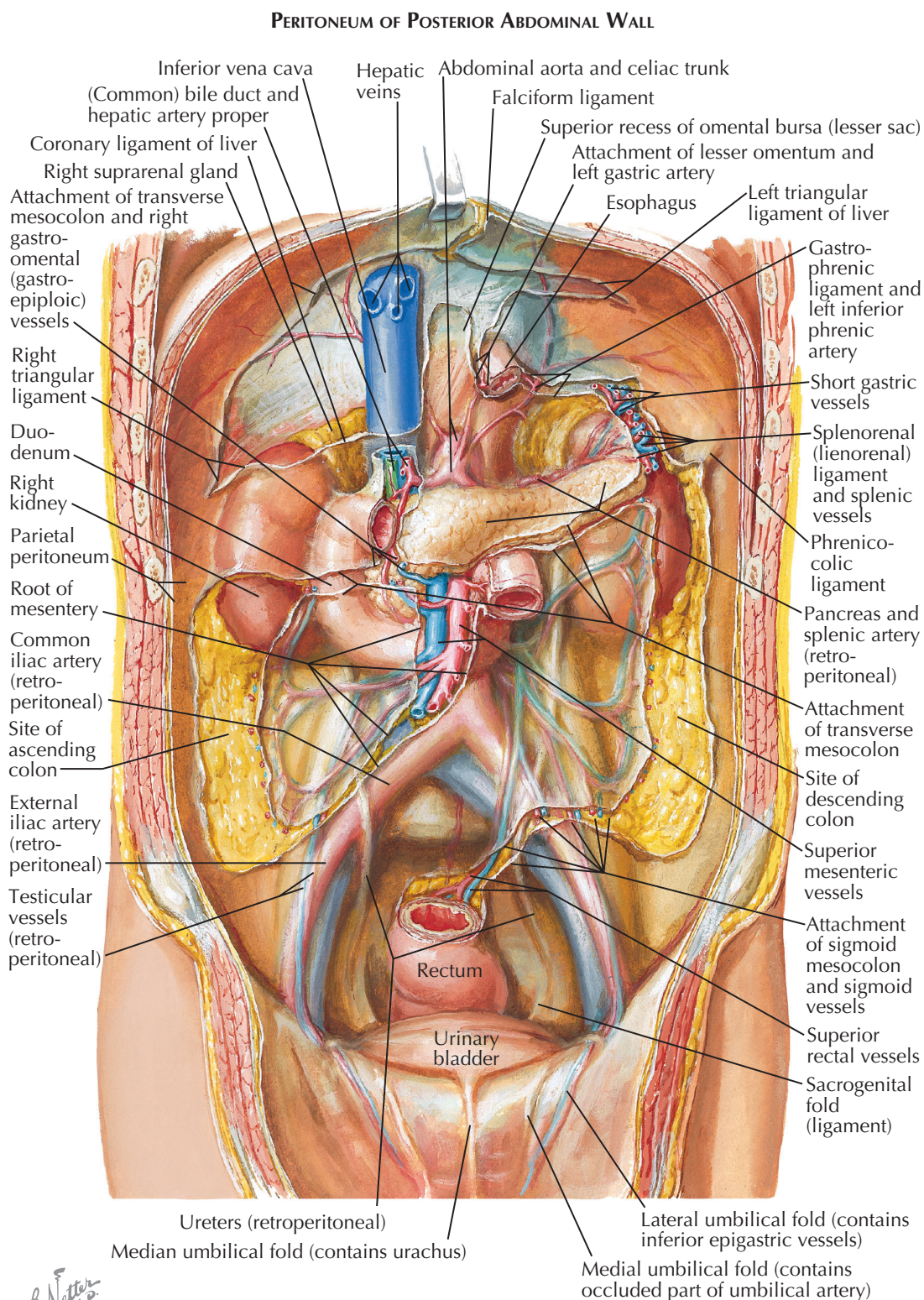
In tracing peritoneum in a horizontal section at about the level of the umbilicus, one can start at the midline of the inner surface of the anterior abdominal wall and

follow from this point the parietal peritoneum to the left along the inner surface of the wall to the posterior wall, where it reflects onto the left side of the *descending colon* to cover also the anterior surface and right side of this structure, from which it passes to the posterior body wall. In early development the descending colon was suspended by the primitive dorsal mesentery, but peritoneal fusion during embryologic development brings it into the adult relationship to the peritoneum just described. The peritoneum continues to the right on the posterior body wall to about the midline, where it reflects forward to form the left (inferior) layer of the intestinal mesentery. The small intestine is completely surrounded (except at its mesenteric attachment) in the free margin of the mesentery; from here the peritoneum is traced posteriorly to the posterior body wall as the right (superior) layer of the mesentery. Thereafter, the peritoneum can be followed to the right onto the posterior body wall, until it reflects from here to cover the left, anterior, and right surfaces of the *ascending colon*. This structure was also suspended originally by the primitive dorsal mesentery. From the right side of the ascending colon, the peritoneum passes to the posterior body wall and then forward on the inner surface of the anterolateral abdominal wall until it reaches the midline, from where the tracing was started. Also in a

PERITONEUM (Continued)

section at about the level of the umbilicus, one would expect to find the greater omentum cut, which is present as an island of peritoneum not connected in this section to the rest of the peritoneum. If the transverse colon is hanging low enough, it too would be cut as an island with its peritoneum continuous with that of the greater omentum.

Worthwhile additions to the general concept of the distribution of the peritoneum, gained by tracing it in several planes as done above, can be obtained by careful study of a view of the posterior half of the abdominopelvic cavity, in which all of the viscera (except the bladder and rectum) that invaginate the peritoneum to any degree have been removed, cutting the peritoneum along its lines of reflection from the posterior body wall or the anterior surfaces of the viscera and vessels that do not project into the peritoneum. The *right* and *left kidneys*, the *pancreas* (except for the tip of its tail), the *second, third*, and most of the *fourth parts of the duodenum*, and the *aorta* and *inferior vena cava* do not project into the peritoneal cavity to a significant degree. The peritoneum covers the inner surface of the abdominopelvic body walls as parietal peritoneum, except where it is lifted away from them by the structures just listed (the bare area of the liver against the diaphragm, the ascending and descending colon, the roots of the mesentery, the transverse mesocolon and sigmoid mesocolon, the ureters and inferior mesenteric vessels, and the rectum and bladder and, in the female, the uterus and broad ligaments, other folds in the pelvis, and folds on the inner surface of the anterior abdominal wall). The folds on the inner surface of the anterior abdominal wall are the *falciform ligament* of the liver (a remnant of the ventral mesentery, ventral to where the liver grew into it), running superiorly and a little to the right from the umbilicus, with the *ligamentum teres* (obliterated umbilical vein) of the liver in its free margin; the *median umbilical fold*, projecting from the superior aspect of the urinary bladder, running superiorly up the midline to the umbilicus; the *medial umbilical folds*, also running to the umbilicus and containing the obliterated right and left umbilical veins; and the right and left *lateral umbilical folds*, containing the *inferior epigastric artery and vein* on each side (which may produce a slight elevation reminding of a fold by pulling the peritoneum a little away from the body wall). The depression between the *median* and *medial umbilical folds* is called the



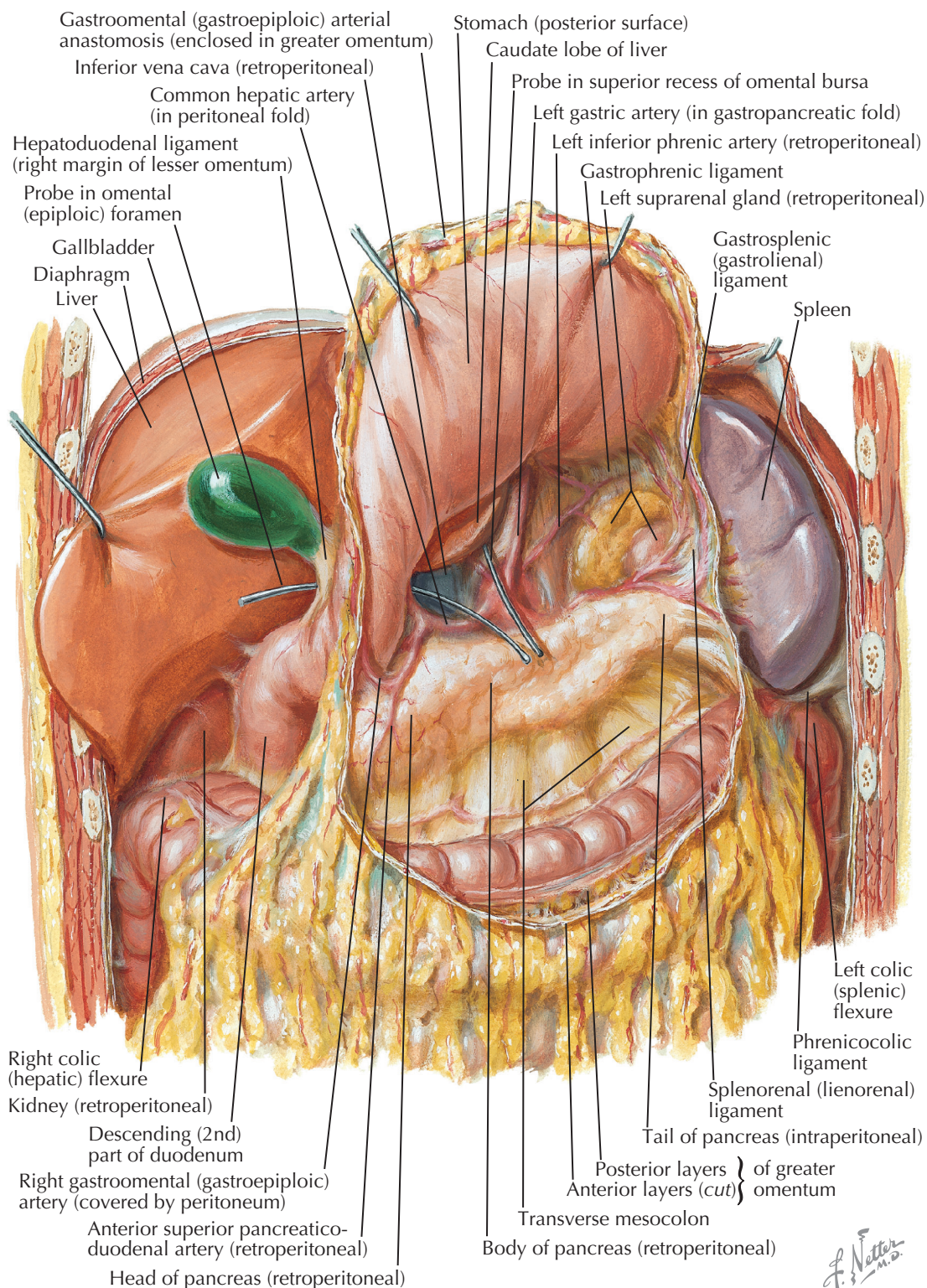
supravesical fossa, whereas the one between each medial and lateral umbilical fold is the epigastric fold. Lateral of the lateral umbilical fold is the lateral inguinal fossa. Parietal peritoneum is thus seen to be applied to practically the entire extent of the inner surface of the anterolateral abdominal wall, and virtually any incision through this wall will open into the peritoneal cavity.

Much of the diaphragm has parietal peritoneum on its abdominal surface, but much less of the muscular portion of the posterior abdominal wall is directly lined

by peritoneum on its inner surface. This is because several viscera, major vessels, and a significant amount of adipose tissue lie behind the peritoneum and most of the abdominal viscera project from the posterior wall into the peritoneal cavity.

From the preceding description it is obvious that the degree to which the various abdominal viscera are covered by peritoneum (visceral peritoneum) varies along a spectrum in which peritoneum may cover just part of one surface of the viscus in question to the other

OMENTAL BURSA: STOMACH REFLECTED



PERITONEUM (Continued)

extreme in which peritoneum covers the viscus entirely, except for the area of attachment of a suspending double-layered fold of peritoneum. "Retroperitoneal" is a very commonly used descriptive term having the general meaning of "behind the peritoneum," which is well agreed upon, but some authors refer to certain organs as retroperitoneal that other authors would not designate in this fashion. Generally, "primarily retroperitoneal structures" (e.g., ureter, kidney) are those that develop posterior to the peritoneal lining and never develop a mesentery. "Secondarily retroperitoneal structures" once had a mesentery but lost it when the organ was laid back along the body wall and the mesentery fused to a degree with the parietal peritoneum (e.g., ascending colon, second portion of the duodenum). "Intrapertitoneal structures" are those that are suspended from the posterior body wall by a mesentery containing blood vessels and nerves associated with the organ (e.g., stomach, ileum). Additional details will be given in the sections dealing with each organ or region.

The *mesentery* is commonly taken to mean the mesentery of the small intestine (i.e., the jejunoileal portion of the small intestine which is the portion having a mesentery or a double-layered fold of peritoneum suspending it from the posterior abdominal wall). The *root of the mesentery* is about 15 cm in length, and its line of attachment varies a bit with the shape of the duodenum, but, in general, it courses from a little to the left of the second lumbar vertebra inferiorly and to the right, crossing the third part of the duodenum, the aorta, the inferior vena cava, the right ureter, and the right psoas major muscle to reach a point near the right sacroiliac joint. The free or unattached border, which contains the loops of the small intestine, is frilled out to such an enormous degree that it may attain a length varying from 3 m to more than 6 m. The distance from the attached border to the free border measures 15 to 22 cm; it may definitely increase with age, probably owing to stretching of the mesentery due to laxity of the anterior abdominal wall. Between the two layers of peritoneum on the two surfaces of the mesentery are the *superior mesenteric artery* and its branches, the accompanying *veins*, lymphatics, approximately 100 to 200 lymph nodes, autonomic nerve plexuses, connective tissue, and varying amounts of adipose tissue, which is present in greater amounts near the root. The mesentery divides the area below the transverse mesocolon into two compartments, which are important in

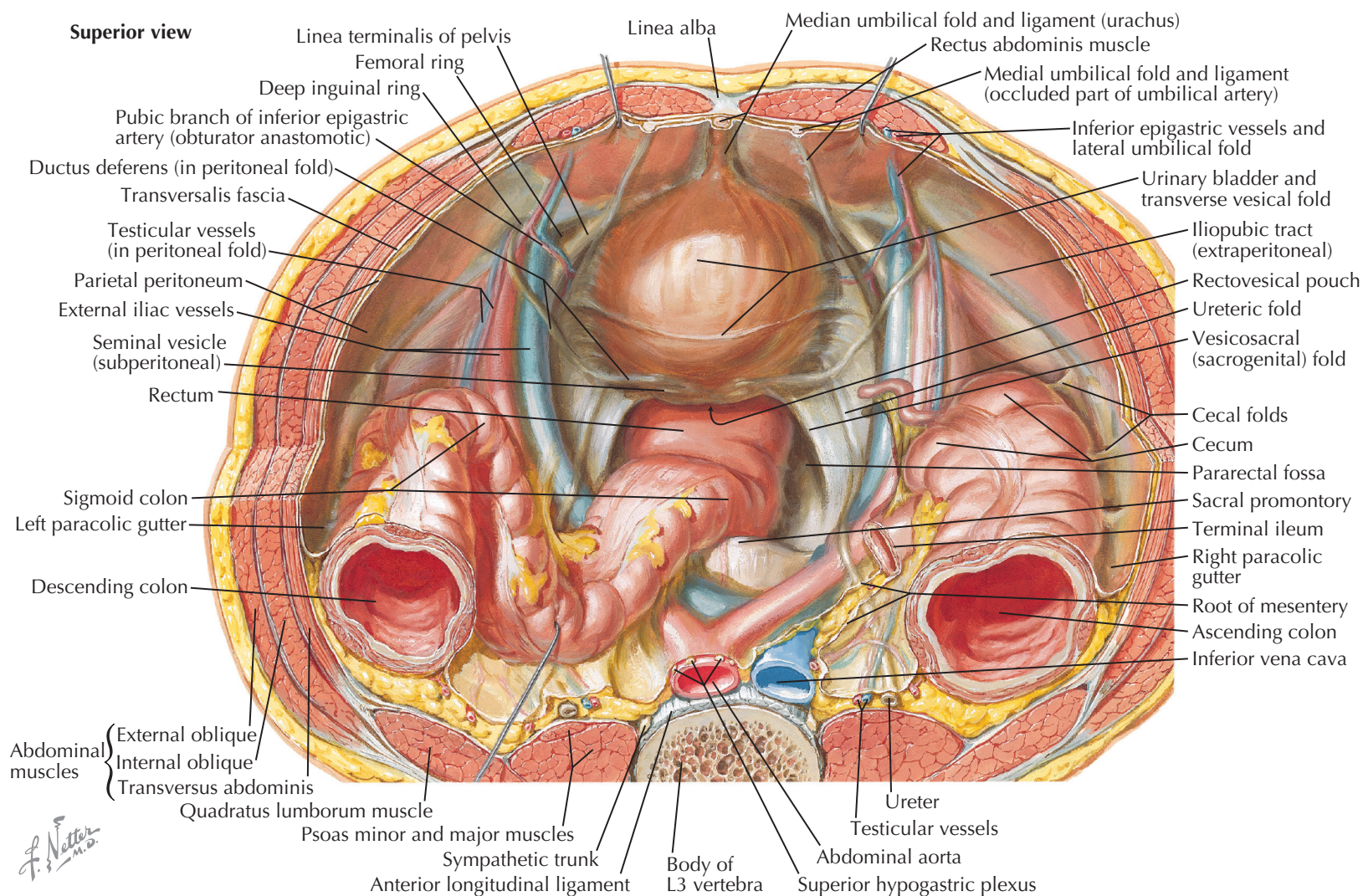
determining collections of fluid and the localization of infection.

The *transverse mesocolon* is the broad peritoneal fold suspending the transverse colon from the posterior body wall. The *root of the transverse mesocolon* crosses the anterior surface of the right kidney, the second portion of the duodenum, and the head of the pancreas, and then passes along the lower border of the body and tail of the pancreas superior to the duodenojejunal flexure, to end on the anterior surface of the left kidney. It

contains the middle colic artery, branches of the right and left colic arteries, accompanying veins, lymphatic structures, autonomic nerve plexuses, as well as a considerable thickness of connective tissue.

The *sigmoid mesocolon* is the mesentery of the sigmoid colon. When the peritoneum begins to surround the large intestine near the crest of the ilium, the attachment of the sigmoid mesocolon follows a fairly straight line from the posterior part of the left iliac fossa inferiorly and medially to reach the third sacral segment.

PELVIC CONTENTS: MALE



PERITONEUM (Continued)

If, as is the case in the other extreme of the range of variation, the colon is closely bound down in the iliac fossa, the line of attachment of the sigmoid mesocolon goes posteriorly along the pelvic brim until it crosses the anterior side of the sacroiliac joint, and then descends along the anterior aspect of the sacrum to the level of its second to third segment. The sigmoid colon is enwrapped by the free margin of the sigmoid mesocolon, which has its greatest width (distance from attached to free border) at its attachment to the first sacral segment. This width varies from about 5 to 18 cm, although it occasionally may be as much as 25 cm between the layers of the sigmoid mesocolon through which run the sigmoidal and superior rectal arteries, accompanying veins, lymphatics and autonomic nerve plexus, and connective tissue, which, of course, includes varying amounts of adipose tissue.

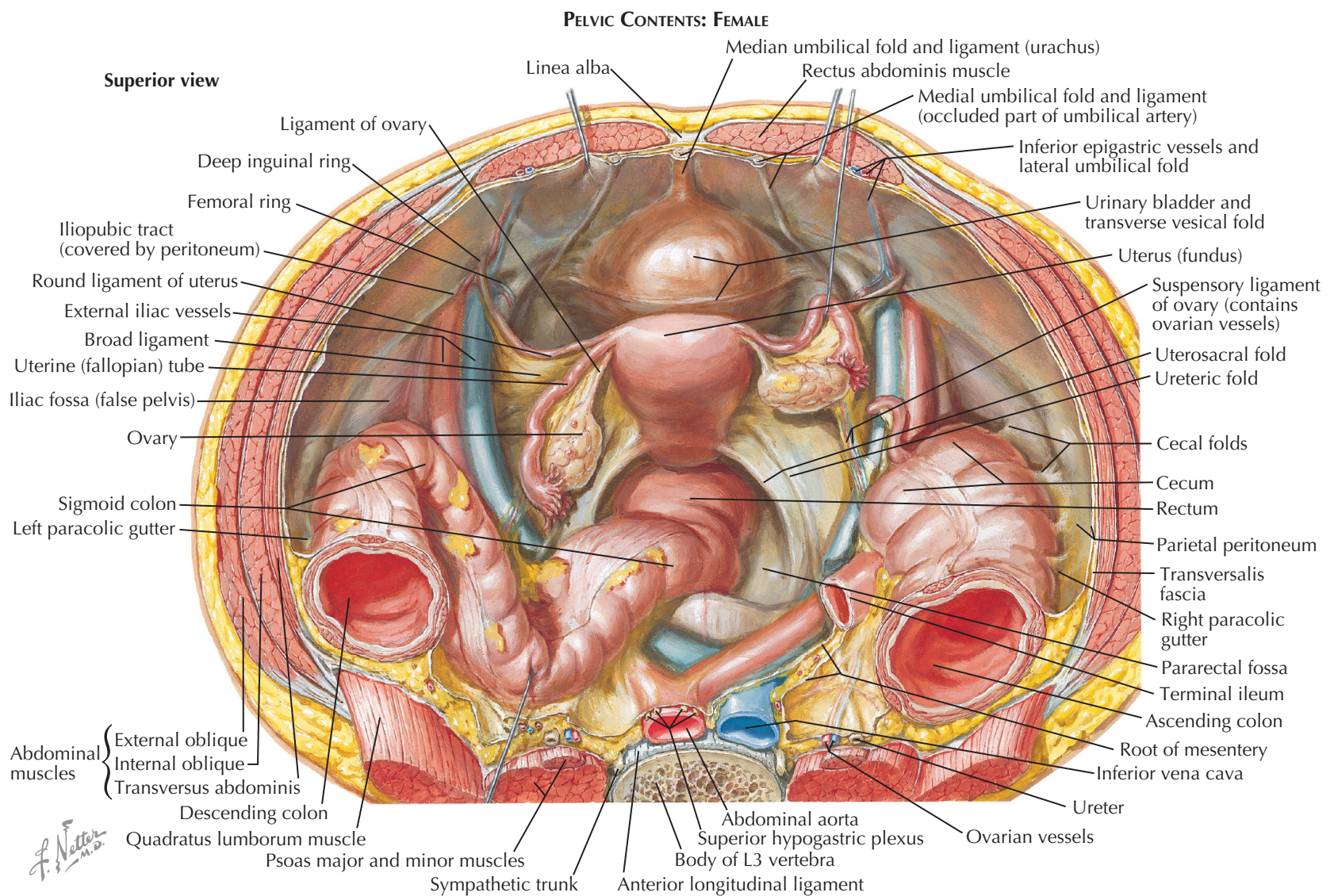
The *greater omentum* is the largest peritoneal fold; it may hang down like a large apron from the greater curvature of the stomach in front of the other viscera as far as the brim of the pelvis or even into the pelvis. It may even extend into an inguinal hernia, most com-

monly on the left side. It also may be much shorter than this, appearing as just a fringe on the greater curvature of the stomach, or it may be of some length and found folded in between coils of the small intestine, tucked into the left hypochondriac area or turned superiorly just anterior to the stomach. The superior end of the left border is continuous with the gastrosplenic ligament, and the superior end of the right border extends as far as the beginning of the duodenum. The greater omentum is usually thin, with a delicate layer of fibroelastic tissue as its framework, and somewhat cribriform in appearance, although it usually contains some adipose tissue and may accumulate a large amount of fat in an obese individual. In the make-up of the greater omentum, the peritoneum of the omental bursa on the posteroinferior surface of the stomach and the greater sac peritoneum on the anterosuperior surface of the stomach meet at the greater curvature of the stomach and course inferiorly to the free border of the greater omentum, where they turn superiorly to the transverse colon. Early in development, these two layers of elongated dorsal mesogastrium course superiorly in front of the transverse colon and transverse mesocolon to the anterior surface of the pancreas. Owing to fusions of these two layers of peritoneum to each other and to the

peritoneum on the transverse colon, and the anterior surface of the primitive transverse mesocolon, it appears, in the fully developed state, as though the "two layers" of peritoneum, running superiorly as the posterior layer of the greater omentum, separate from each other to surround the transverse colon and continue as the two layers of the transverse mesocolon. Frequently, there is enough fusion in the four-layered primitive greater omentum inferior to the transverse mesocolon that no extension of the omental bursa is present between layers. Close to the greater curvature of the stomach, the right and left gastroepiploic vessels course, anastomosing with each other in the greater omentum. The greater omentum, if of any length, has a great deal of mobility and can shift around to fill what would otherwise be temporary gaps between viscera or to build up a barrier against bacterial invasion of the peritoneal cavity by becoming adherent at a potential danger spot.

The *lesser omentum*, which can be subdivided into *hepatogastric* and *hepatoduodenal ligaments*, extends from the posteroinferior surface of the liver to the lesser curvature of the stomach and the beginning of the duodenum. It is extremely thin, particularly the part to the left, which is sometimes fenestrated. The right side is

PELVIC CONTENTS: FEMALE



PERITONEUM (Continued)

thicker and ends in a free, rounded margin, which contains the common bile duct to the right, the hepatic artery to the left, and the portal vein posterior to these two, and forms the anterior border of the omental foramen. In addition to the structures just listed, the lesser omentum contains the right and left gastric arteries (close to the lesser curvature of the stomach) and the accompanying veins, lymphatics, and autonomic nerve plexuses. The lesser omentum reaches the liver at the porta hepatis, and to the left of the porta hepatis it extends to the bottom of the fossa for the ligamentum venosum, the obliterated ductus venosus, which carried oxygenated blood from the umbilical vein to the inferior vena cava.

The *omental bursa* (lesser sac of the peritoneum) is a large fossa, or outpouching, from the general peritoneal cavity. It is bounded in front, from superior to inferior, by the *caudate lobe of the liver*; lesser *omentum*, *posteroinferior surface of the stomach*, and *anterior layer of the greater omentum* (at least in part). Posteriorly, from inferior to superior, are the posterior layer of the greater omentum (the amount of this depends on the variable inferior extent of the bursa), *transverse colon*,

anterior layer of the *transverse mesocolon*, anterior surface of the *pancreas*, *left suprarenal gland*, superior end of the *left kidney*, and, to the right of the esophageal opening into the stomach, that part of the diaphragm supporting the caudate lobe of the liver. The horizontal extent of the bursa stretches from the omental foramen at the right to the hilum of the spleen at the left, where it is limited by the *splenorenal* and *gastrosplenic ligaments*. Inferiorly, the bursa may extend about as far as the transverse colon, its cavity having originally reached as far down as the free margin of the greater omentum before becoming obliterated by fusion of its layers. The portion of the bursa between the caudate lobe of the liver and the diaphragm is called the superior recess, and the narrow portion from the omental foramen across the head of the pancreas to the gastropancreatic fold is called the vestibule of the bursa.

The *omental foramen* (of Winslow) is the opening by which the omental bursa communicates with the general peritoneal cavity (greater sac). It is somewhat circular and is usually large enough to admit one or two fingers. Anterior to the foramen is the free margin of the lesser omentum, containing the *common bile duct*, *hepatic artery*, and *portal vein*. Its posterior border is the peritoneum covering the inferior vena cava; superior to

it is the peritoneum on the caudate process of the liver, and its inferior boundary is the peritoneum that covers the beginning of the duodenum and the hepatic artery.

Many extremely variable and inconstant fossae or recesses have been described which are of interest to the surgeon because of the possibility of herniation of a loop of intestine into any one of them. The more common ones are located either in the region of the fourth portion of the duodenum or in the region of the cecum and ileocecal junction. A relatively common "intersigmoid recess" is found on the left side of the line of attachment of the sigmoid mesocolon at the angle that is present in this line when the colon is tightly bound down in the iliac fossa.

A characteristic of the peritoneum covering the surfaces of the various parts of the colon is the presence of little outpouchings of peritoneum containing adipose tissue, which are called omental appendages (*appendices epiploicae*).

The parietal peritoneum is supplied by the nerves to the adjacent body wall and is thus pain sensitive. The visceral peritoneum is insensitive to ordinary pain stimuli but does respond to ischemia, distention, and inflammation. When moist surfaces of peritoneum which are in contact become irritated, adhesions tend to form that often become permanent.

PELVIC FASCIA AND PERINEOPELVIC SPACES

The steadily changing pressure and filling conditions in the pelvis require adaptability of those structures that support the viscera within the funnel-like frame of the pelvis. Part of this support derives from the anorectal musculature and the levator ani. But since these muscles are, to a great extent, involved in the sphincteric and emptying functions of the anorectal canal, their supporting tasks are assisted by the connective tissue structures of the pelvic fascia, which have substantial tensile strength. The anatomic relationships of the pelvic fascia and associated muscles are physiologically and surgically significant. The pelvic fasciae are divisible into a visceral and a parietal portion. The former lies entirely superior to the pelvic diaphragm, forming the fascial investments of the pelvic viscera, the perivascular sheaths, and the interspersal and pelvovisceral ligaments, which are described below.

The parietal portion of the pelvic fascia may be divided into parts that lie either superior or inferior to the levator ani muscle. Superior to the levator ani, parietal pelvic fascia is a continuation of the parietal abdominal fascia. The *iliopsoas fascia* and the *transversalis fascia* of the abdomen are attached along the *linea terminalis* to the bony pelvis and then extend inferiorly into the pelvis over the inner surface of the *obturator internus muscle* as the *obturator fascia*. Anteriorly, the transversalis fascia is attached to the inner surface of the pubic bones and symphysis. The prevertebral fascia of the abdomen continues inferiorly into the pelvis as the *presacral fascia*.

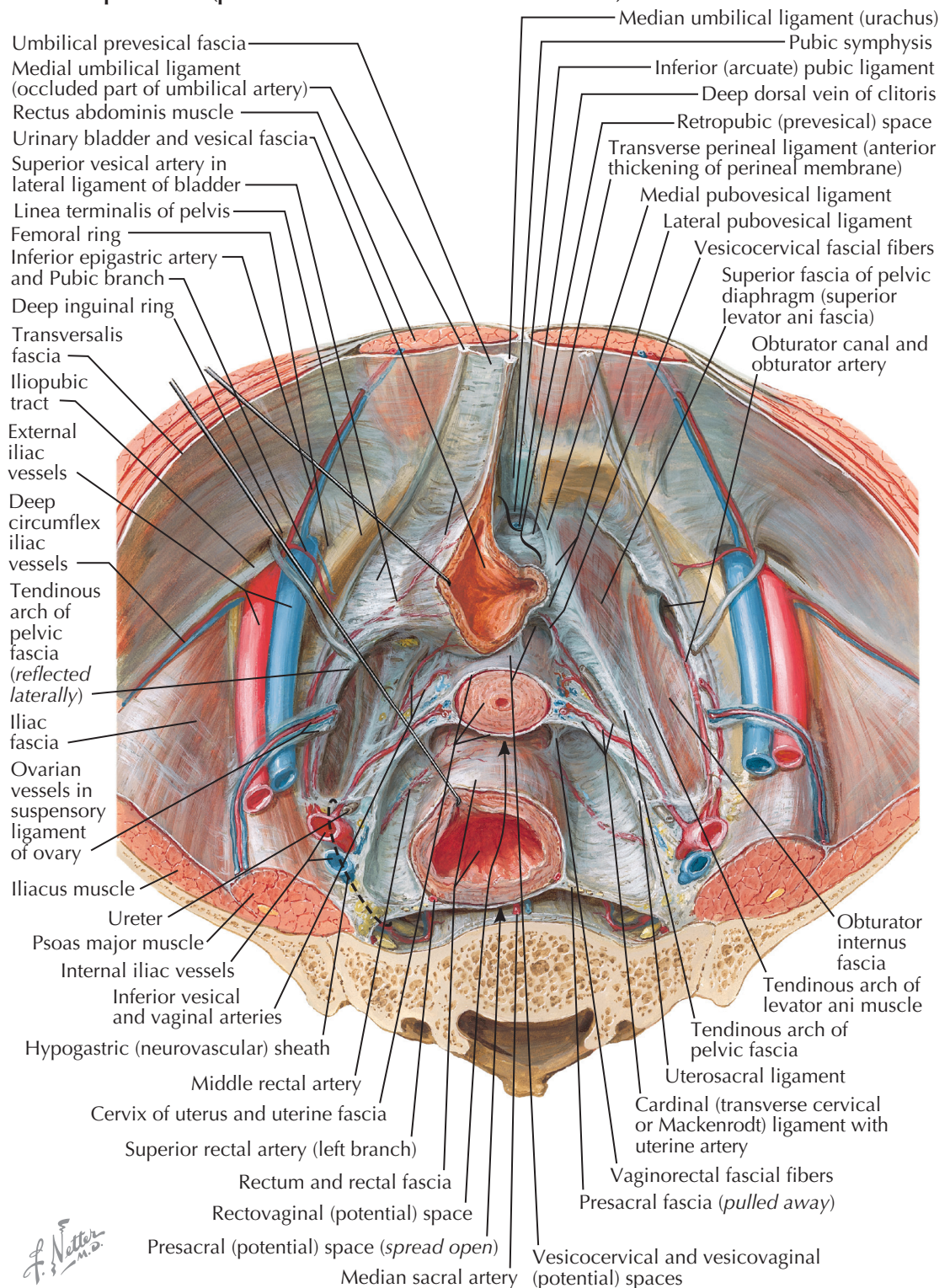
The superior layer of the pelvic diaphragm arises from the *arcus tendineus* of the levator ani muscle, which is a thickening in the obturator fascia, running arc-wise and convex inferiorly from the posterior surface of the pubic ramus (1 or 2 cm in front of the obturator foramen) to a point just superior to the ischial spine. From this arcus, the *superior fascia of the pelvic diaphragm* spreads out to cover the superior (inner) surface of the levator ani and coccygeus muscles.

Anteriorly, this fascia spans the infrapubic interval in front of the *transverse perineal ligament*. The fascia descends just a few millimeters to form a small fossa, the bottom of which is pierced by the *dorsal vein of the penis* or *clitoris*, respectively. On each side of this small fossa, a thickening in the fascia extends posteriorly from each side of the lower end of the symphysis pubis to the prostate in the male and to the bladder in the female. These thickened parts are the medial puboprostatic ligaments (or anterior true ligaments of the prostate) in the male, to which correspond the *medial pubovesical ligaments* (pubourethral or anterior true ligaments) of the bladder, in the female. The lateral puboprostatic or pubovesical ligaments (or lateral true ligaments of prostate or bladder) lie just posterior to this and consist of lateral reflections from the fascia to the prostate or bladder, respectively.

The thickenings in the superior fascia of the pelvic diaphragm, which make up the medial puboprostatic or

ENDOPELVIC FASCIA AND POTENTIAL SPACES

Female: superior view (peritoneum and loose areolar tissue removed)



pubovesical ligaments, continue backward in a slight curve, concave downward, gradually diverging to the region of the ischial spine. This constitutes on each side the *arcus tendineus of the pelvic fascia*, which lies considerably more medially and below the *arcus tendineus of the levator ani*. The superior fascia of the pelvic diaphragm also continues medially and below its arcus tendineus. Anterior to the rectum, it spans the interval between the crura of the pubococcygeus muscles and, coursing

around their free margins, fuses with the deep (superior) layer of the urogenital diaphragm. Here also it is reflected upon the prostate and bladder in the male and the vagina in the female as the visceral fascial sheaths of these respective organs.

Posteriorly, the superior fascia of the pelvic diaphragm surrounds the rectum as it passes through the pelvic diaphragm. It is reflected there as a sheath upon the rectum as the *visceral (rectal) fascia*, but it also blends

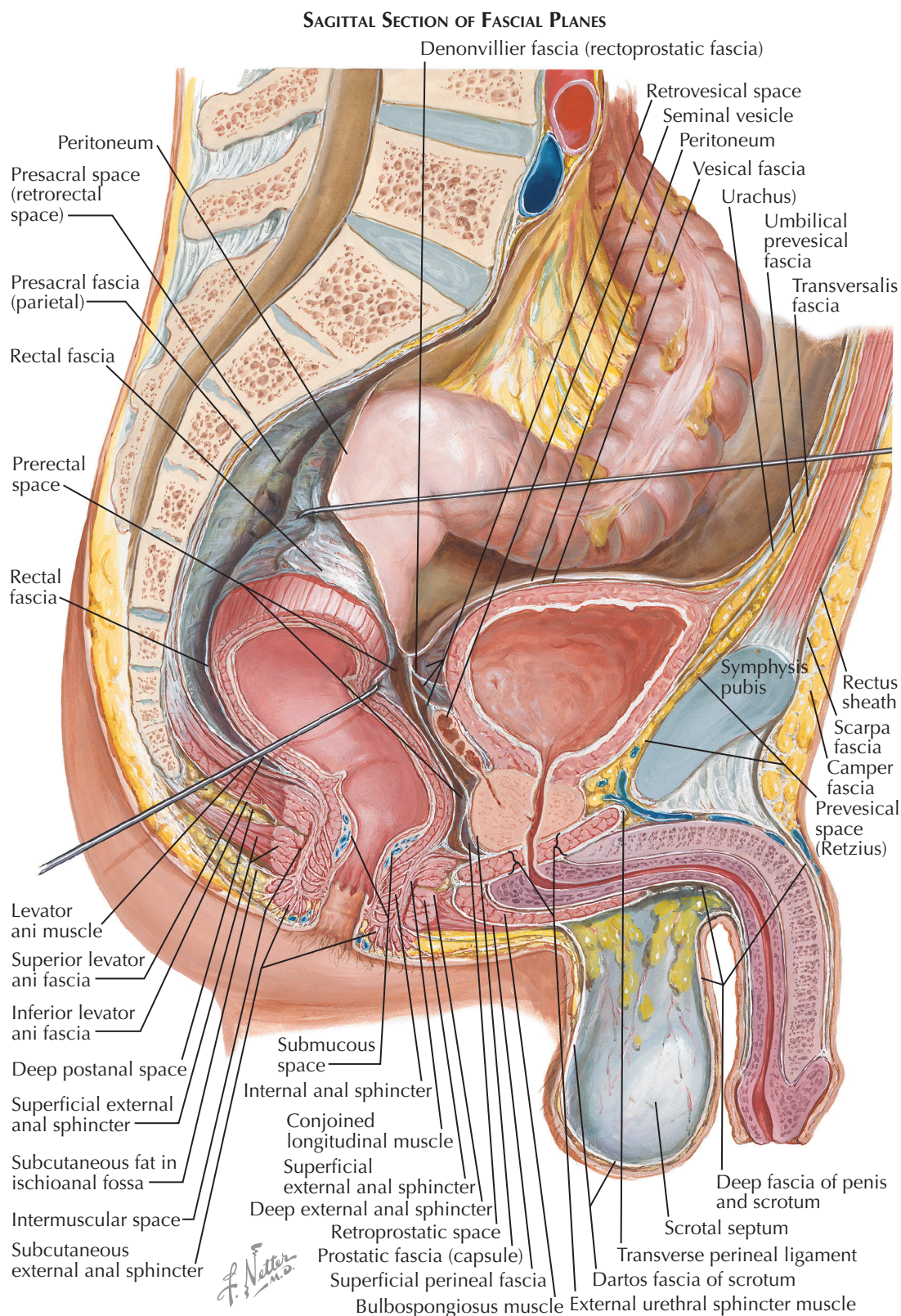
PELVIC FASCIA AND PERINEOPELVIC SPACES (Continued)

with the longitudinal rectal musculature and contributes fibrous extensions to the formation of the fibromuscular, conjoined longitudinal muscle of the anal canal. The reflection takes place largely at the arcus tendineus of the pelvic fascia, but also more medially and more inferiorly in the region where the viscera begin to penetrate the pelvic diaphragm.

Inferior to the levator ani, the obturator fascia continues inferiorly on the medial walls of the pelvis below the arcus tendineus of the levator ani muscle. It covers the obturator internus muscle and is attached to the bony pelvis about the margins of that muscle. In its lower portion the fascia is split to form the more-or-less horizontal *pubendal canal* (*Alcock canal*), in which course the *internal pudendal vessels* and the *pudendal nerve*. Depending on when it leaves the pudendal nerve, the canal may also include the *dorsal nerves of the penis*. The *inferior fascia of the pelvic diaphragm* is a comparatively thin sheet that extends from the arcus tendineus of the levator ani muscle and covers the inferior surface of this and the coccygeus muscle. It continues around the lower rectum and the anal canal. It is reflected into the anterior recess of the *ischioanal fossa*.

The perineal fascia consists of a superficial subcutaneous and a deep membranous layer. The former is continuous with the subcutaneous fat (*Camper fascia*) of the abdominal wall; the latter is the *superficial perineal fascia* (*Colles fascia*), corresponding to the Scarpa fascia of the abdomen. The superficial layer varies considerably throughout the perineum. Over the anal triangle it forms the fatty layer of the *deep part of the ischioanal fossa*, whereas laterally over the ischial tuberosities, it is made up of fibrous fascicles that connect to the underlying bone and form, directly over the ischial tuberosities, fibrous bursal sacs. The main part of the superficial perineal fascia has a firm attachment to the pubic rami and to the posterior margin of the *urogenital diaphragm*. It spreads medially across the urogenital triangle, constituting the floor of the *superficial perineal space*, which lies between it and the inferior layer of the urogenital diaphragm and contains the superficial perineal musculature.

The visceral fascia invests, one by one, each of the pelvic organs, forming their fascial capsule (e.g., *vesical fascia*, *prostatic fascia*, *vaginal-uterine fascia*, *rectal fascia*). It also contains the ligaments that connect these viscera with each other and with the pelvic walls and floor, as well as the perivascular sheaths. The latter consist of the *hypogastric sheath*, which arises on each side from the parietal pelvic fascia over a roughly triangular area in the posterolateral angle of the pelvis and extends inferiorly to the spine of the ischium. This sheath contains the *internal iliac vessels* (and a variable number of their branches) and the *ureter*, as well as its accompanying nerves and lymphatics. Anteriorly, the sheath is continuous with the *tendinous arch of the pelvic fascia*, which



extends anteriorly to the superolateral border of the bladder, where it splits into superior and inferior layers. These blend, respectively, with the superior and lateral aspects of the vesical fascia. Anteriorly, the arch carries the *obliterated umbilical artery* and *superior vesical vessels* to the urinary bladder as the *lateral ligament of the bladder*. Posteriorly, in the female, the hypogastric sheath fuses with the *suspensory ligament of the ovary* containing the *ovarian vessels*.

The *uterosacral ligament* extends inferiorly from the hypogastric sheath. Laterally, it blends with the superior fascia of the levator ani and medially with the inferolateral aspects of the bladder or prostatic fascial capsule. In a sense, it thus constitutes a reflection from the superior fascia of the levator ani to the vesical (visceral) fascia along the *tendinous arch of the levator ani*, its anterior portion containing the lateral true ligaments of the bladder or prostate. Posteriorly, the transversely

PELVIC FASCIA AND PERINEOPELVIC SPACES (Continued)

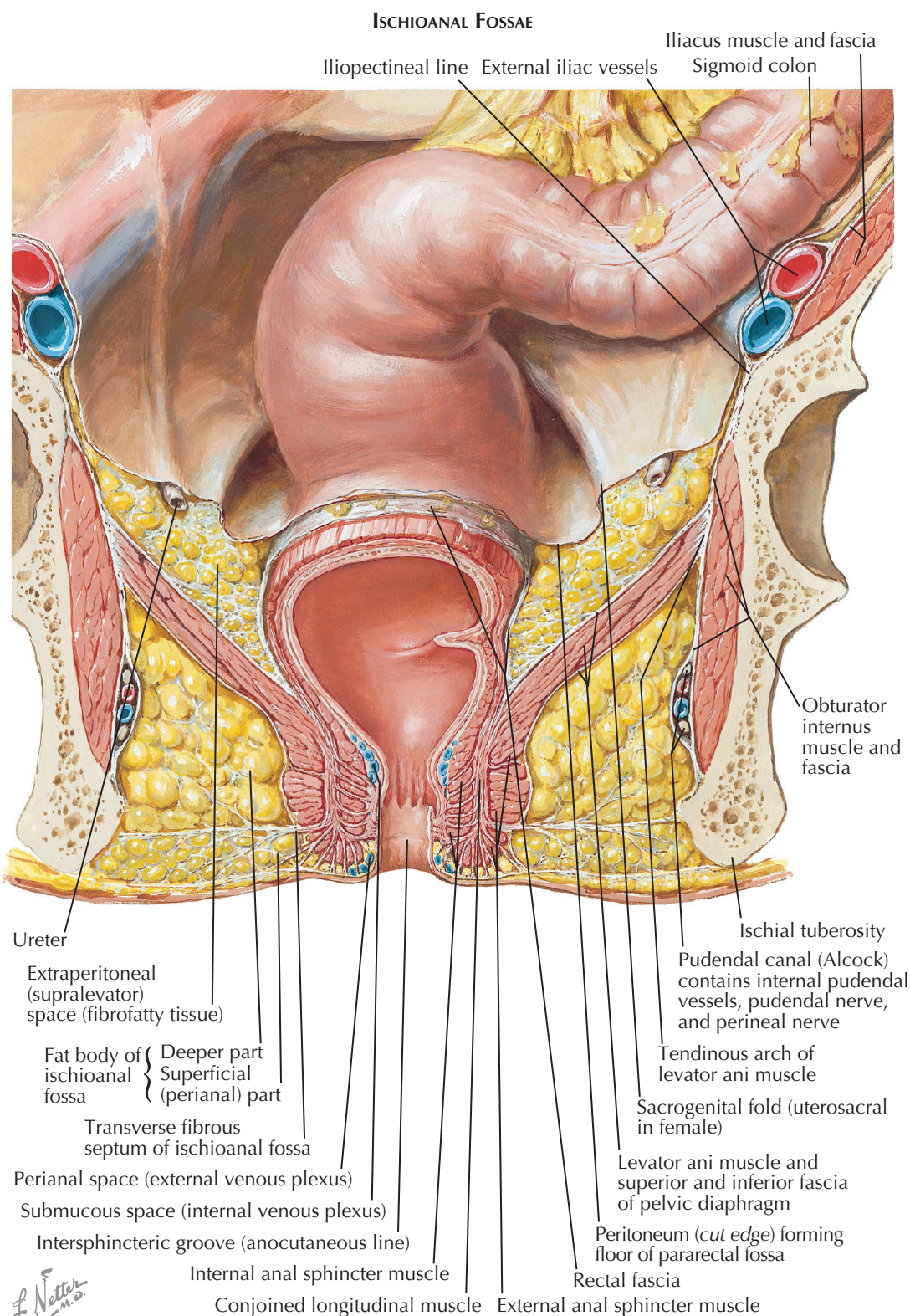
placed *transverse cervical (cardinal) ligament* of the uterus extends from the uterosacral ligament, carrying the *ureter*, *inferior vesical vessels*, *uterine vessels*, and autonomic nerves.

The *presacral fascia* extends medially from the hypogastric sheath sitting anterior to the sacrum and *anterior sacrococcygeal ligament*, lying in a more or less vertical plane, in contrast to the superior and inferior wings, which unfold in a nearly horizontal plane. Upon reaching the sides of the rectum, the presacral fascia splits into two leaves that encircle the rectum as the rectal (visceral) fascia. This fascia carries the *superior* and *middle rectal vessels*, inferior hypogastric or pelvic nerve plexus, and many lymphatics.

The course of the pelvic muscles and the anorectal musculature, together with the superior and inferior fascia of the levator ani, give rise to a number of *perineopelvic spaces*, which require more than mere anatomic recognition because they have a fundamental importance for an adequate concept of infectious and malignant processes of the pelvis and perineum. As with the fasciae, these spaces are conveniently separated by the levator ani muscle. Superior to the levator ani, in the male, there are four main spaces: (1) the *prevesical space* (of Retzius), (2) the *rectovesical space*, (3) the bilateral *pararectal spaces*, and (4) the *retrorectal space*.

The *prevesical space of Retzius* is, in both sexes, a potentially large cavity surrounding the anterior and lateral walls of the bladder. The main cavity in front of the bladder contains two superimposed anteromedian recesses and two lateral compartments. The upper anteromedial recess lies posterior to the anterior abdominal wall (i.e., behind the most medial parts of the *transversalis fascia*) and is roofed by the peritoneal reflection from the dome of the bladder supported by the *urachus* and the *umbilical prevesical fascia*. Its lateral borders are demarcated by the *obliterated umbilical arteries*. The lower recess, continuous with the one above, lies posterior to the symphysis and pubic bones, anterior to the bladder, with a floor formed by the pubovesical ligaments in the female or the puboprostatic ligaments in the male. The lateral recesses of the prevesical space are bounded by a lateral wall formed by the obturator fascia and the superior fascia of the levator ani, and a median wall presented by the bladder and the lateral ligaments of the bladder. They contain the ureter and the main neurovascular supply to the bladder and, in the male, the prostate. The floor of the lateral recess is the superior fascia of the levator ani. Posteriorly, the lateral recess of the prevesical space extends to the hypogastric sheath in the region of the ischial spine. The roof is formed by the tendinous arch of pelvic fascia covered by the peritoneum, where these tissues are reflected from the lateral pelvic wall.

The *retrovesical compartment* in the male, divisible into three subspaces, lies between the bladder and the prostate, covered by the vesical and prostatic fasciae anteriorly, and the rectal fascia covering the rectum posteriorly. Its roof is formed by the *rectovesical recess* or pouch of the peritoneum, which comes into existence by the continuity of the peritoneal reflection from the rectum to the bladder. Its floor is the posterior part of



the urogenital diaphragm. The *rectoprostatic (Denonvilliers) fascia*, originating from the undersurface of the rectovesical peritoneal pouch and extending inferiorly in a coronal plane, divides into two leaves, an anterior leaf, blending with the prostatic fascia or capsule, and a posterior leaf, attaching below to the urogenital diaphragm medially and to the hypogastric sheath laterally. Thus the retrovesical compartment can become subdivided into the *retrovesical space* and *retroprostatic space* anteriorly and the *prerectal space* posteriorly. The infe-

rior aspect of the hypogastric sheath marks the lateral boundary of the two anterior spaces and also the separation from the lateral recess of the space of Retzius. Inferiorly, the prerectal space terminates where the *rectal fascia* attaches itself to the urogenital diaphragm or its thin superior fascia. The retroprostatic space (Proust space) terminates inferiorly in the same region but varies, depending on the very inferior limit of the rectoprostatic fascia and its attachments to the prostatic capsule.

PELVIC FASCIA AND PERINEOPELVIC SPACES (Continued)

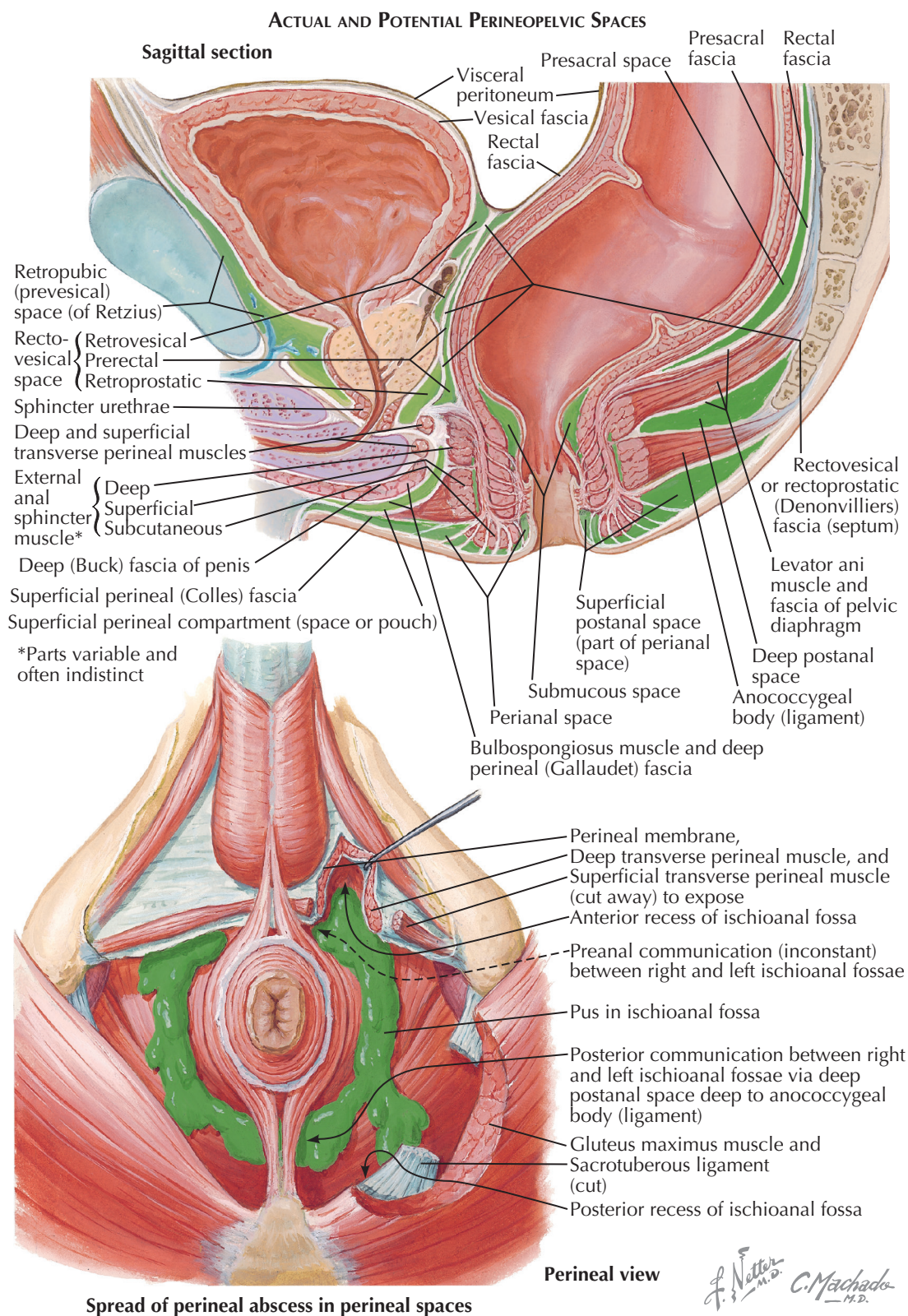
In the female, as in the male, the area between the bladder and the rectum is divided into three spaces. The dominant dividing structure, however, is not the rectoprostatic fascia but the much more substantial vagina, cervix, and uterus. Anterior to these structures, two spaces come into existence, the *vesicocervical space* superiorly and the *vesicovaginal space* inferiorly. They are separated by a fascial septum, the supravaginal septum or vesicocervical ligament, which forms the floor of the vesicocervical space and the roof of the vesicovaginal space. The vesicocervical space is roofed by the uterovesical fold of the peritoneum and extends inferiorly to the point where the urethra and vagina are in apposition superior to the urogenital diaphragm. In the floor of this space, the medial and lateral *pubovesical ligaments* surround the urethra. Laterally, the vesicovaginal space is limited by the strong fascial connections between the bladder and the cervix.

In the female, the *rectovaginal space* is farther from the anterior compartments because the substantial mass of the cervix, uterus, and vagina provide more separation than in the male. Whether or not the small area between the rectum and the genital organs can be divided into a retrovaginal and a *prerectal space* is a controversial question of no practical significance. Of more practical importance is the fact that the rectovaginal space is roofed by a deep peritoneal fold that forms the *rectouterine pouch* (of Douglas). The boundaries of this space are, anteriorly, the *vaginal fascia* and, posteriorly, the *rectal fascia*. Laterally, the space extends to the fusion of the vaginal and rectal fascial collars, which, in this region, form the wings of the vagina. The space terminates inferiorly at the line of fusion between the posterior vaginal wall and the anal canal. In this region numerous fascial and muscular elements fuse, terminating inferiorly at the *perineal body*, also called the "central point of the perineum."

The *pararectal space* extends on each side from the rectoprostatic fascia (male) or the cardinal ligament (female) to the presacral fascia. It lies on the supraanal fascia covering the superior surface of the pubococcygeus muscle, alongside the inferolateral parts of the rectum or its fascial enclosure. Its roof is made up, in both sexes, of the peritoneum reflected from the lateral aspects of the rectum to the pelvic walls, forming the floor of the pararectal peritoneal fossa.

The *presacral space*, similar in both sexes, constitutes the interval between the parietal pelvic fascia, covering the sacrum as well as the piriformis, coccygeus, and pubococcygeus muscles, and the presacral fascia, which envelops the rectum as the *rectal fascia*. Where the posterior rectal wall lies almost horizontally, the ventral lining of the presacral space is produced by the rectal fascial collar. Superiorly, the space becomes continuous with the prevertebral-retroperitoneal areolar tissue. A strong lateral barrier for this space is provided by the attachment of the hypogastric sheath to the parietal fascia, a fact that explains why retrorectal abscesses are more apt to rupture into the rectum than to penetrate into the space superior to the levator ani.

In the spaces inferior to the levator ani, the *submucous space*, encircling the sphincteric portion of the rectum



and extending from the anorectal muscle ring to the dentate line, is the highest or most cranial. Its practical significance is explained by its contents: the terminal anastomotic network of the internal rectal venous plexus and a rich lymphatic plexus, both embedded in a supportive fibroelastic connective tissue.

A potential but not truly anatomic space, with somewhat ill-defined borders, lies within the conjoined longitudinal muscle between the internal and external anal sphincters. This *intermuscular space* surrounds the entire

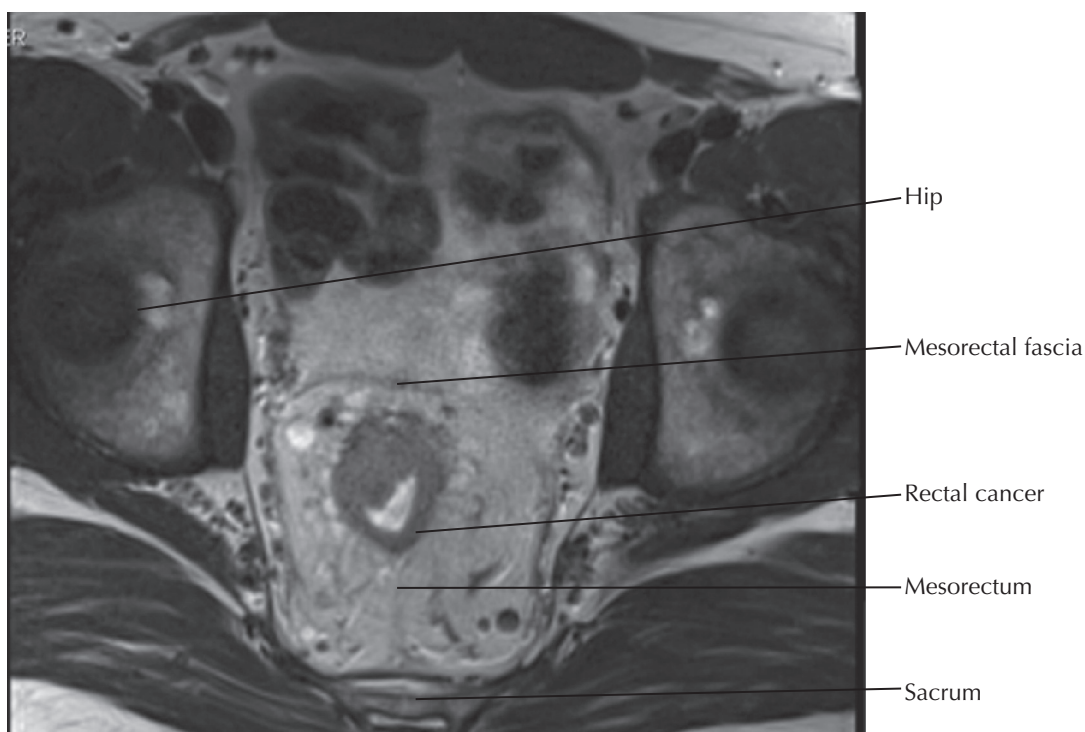
circumference of the anal canal, from the junction of the external sphincter with the levator ani to the intramuscular groove. Abscesses in this intermuscular space may develop as a result of infection of the perianal glands expanding within it. Both the submucous and intermuscular spaces are not interfascial but, rather, intravisceral.

The perianal space is located between the skin and the transverse septum of the ischioanal fossa. Its boundaries, projected to the surface, correspond to the anal

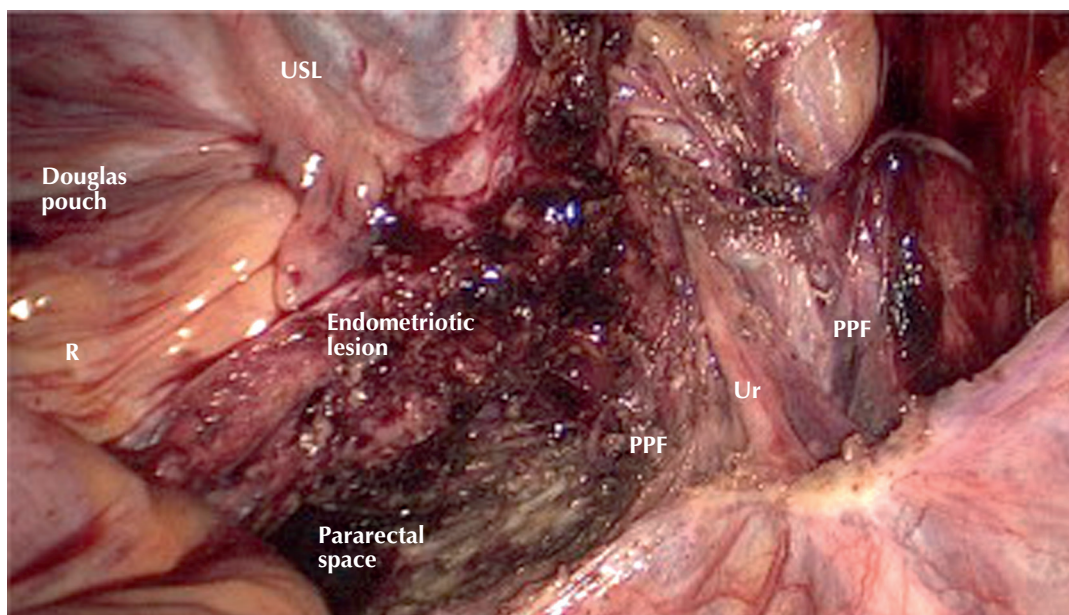
PELVIC FASCIA AND PERINEOPELVIC SPACES (Continued)

triangle. Anteriorly, the space extends to the posterior border of the superficial transverse perineal muscle and laterally as far as the ischial tuberosities. Medially, the perianal space is confined by the anoderm superiorly as far as the latter's firm attachment to the internal anal sphincter. Numerous fibrous extensions from the conjoined longitudinal muscle, which pass through the subcutaneous external anal sphincter, transverse the perianal space. It is important to note that, circumnally, the perianal space reaches to the inferior end of the internal sphincter, within the subcutaneous external anal sphincter. The space contains the external rectal venous plexus and superficial perianal lymphatics. Posteriorly, extending as far as the coccyx, the perianal space changes its name and becomes the *superficial post-anal space*, which extends from the anal canal to the subcutaneous tissue inferior to the extensions of the superficial external anal sphincter, known as the *anococcygeal ligament*, as it attaches to the posterior surface of the coccyx. It is noteworthy that the perianal space of each side communicates with its counterpart of the opposite side via this superficial postanal space inferior to the anococcygeal ligament in just the same fashion as the ischioanal fossae of each side communicate superior to this ligament via the deep postanal space. Posteriorly, the relationships to the extensions of the conjoined longitudinal muscle and the fibers of the corrugator cutis ani confine abscesses and fistulas complicating anal fissures to the superficial tissues.

The largest and most important of the spaces inferior to the levator ani muscle are the paired *ischioanal fossae* (average 6 to 8 cm anteroposteriorly, 2 to 4 cm wide, 6 to 8 cm deep). Each of these is irregularly wedge-shaped, with the apex at the pubic angle and the base at the gluteus maximus muscle. The superomedial wall is formed by the circumanal and infraanal fasciae covering the superficial and deep portions of the external anal sphincter and the superimposed *puborectalis* and *pubococcygeus portions* of the levator ani muscle. The attachments of this muscle and the infraanal fascia to the urogenital diaphragm mark the medial wall of the *anterior extension* (Waldeyer space), which extends anteriorly into the space above the urogenital diaphragm. At the most cranial point of the ischioanal fossa, the inner wall joins the outer wall, which is formed by the *obturator fascia*, overlying the *obturator internus muscle*, and farther inferiorly by the *ischial tuberosity*. The infraanal fascia covering the iliococcygeus muscle is the roof of the ischioanal fossa. The coccyx, sacrospinous ligament, sacrotuberous ligament, and overlapping gluteus maximus muscle constitute the base or posterior wall of the fossa. These structures thus confine the *posterior extension* of the ischioanal fossa, which has, posteriorly to the anal canal, no medial walls. The fossae of each side communicate with each other by what is known as the *deep postanal space*, which lies superior to the anococcygeal ligament or posterior extension of the external anal sphincter and inferior to the levator ani muscle.



Axial MRI showing rectal cancer, surrounding mesorectum, and mesorectal fascia



Surgical view of right extraserosal pelvic fascia resection. **PPF** = parietal pelvic fascia; **R** = right; **Ur** = ureter; **USL** = uterosacral ligament. (From Ballester M, Belghiti J. Surgical and clinical impact of extraserosal pelvic fascia removal in segmental colorectal resection for endometriosis. *J Minim Invasive Gynecol* 2014; 21:1041-1048.)

This deep postanal space is also known as the posterior communicating space, because through it communicate the right and left ischioanal fossae. The deep postanal space is thus the usual pathway for purulent infections to spread from one ischioanal fossa to the other, resulting in the semicircular or "horseshoe" posterior anal fistula. The floor of the ischioanal space posterior to the urogenital diaphragm is the transverse septum of the ischioanal fossa. In the anterior recess the floor is formed by the urogenital diaphragm. The ischioanal

space is filled with adipose tissue in a matrix of thin collagenous fibrils. The inferior rectal vessels and nerves cross each space obliquely from its posterolateral angle en route from the pudendal vessels and nerves in the obturator canal to the anal canal.

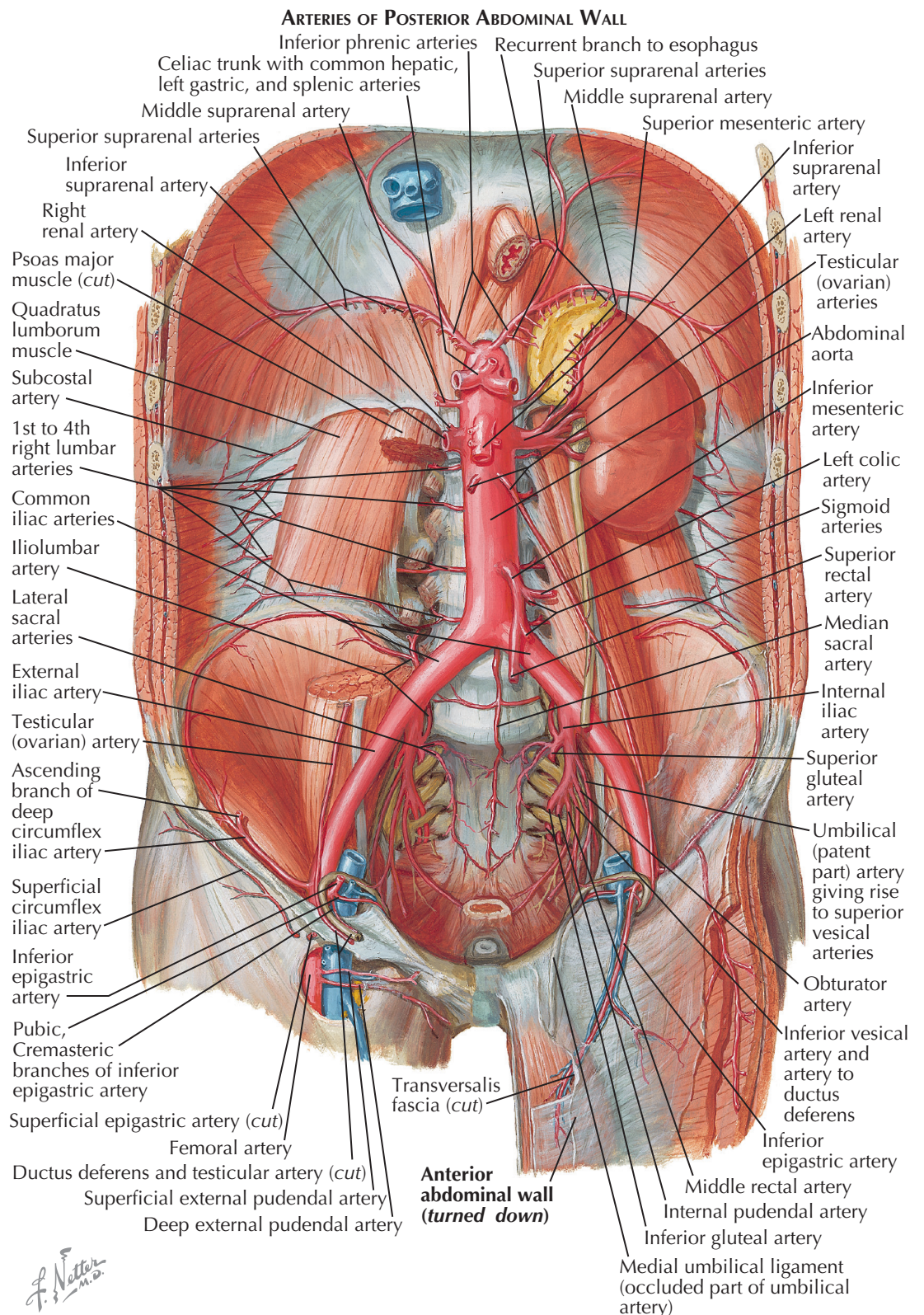
The superficial and deep compartments of the *urogenital diaphragm* occupy the space within the pubic arch and contain the urogenital musculature that is in close functional relationship to the pelvic diaphragm and the anorectal sphincters.

BLOOD SUPPLY OF THE ABDOMEN

The aorta enters the abdomen by passing posterior to the median arcuate ligament of the diaphragm at the level of T12. Its first branches are the paired *inferior phrenic arteries*, which commonly originate between the diaphragmatic crura and course to the inferior aspect of the dome of the diaphragm, where they divide into anterior and posterior branches. The latter of these anastomose with the intercostal arteries, whereas the former anastomose with twigs of the inferior phrenic artery, as well as the *musculophrenic*, *pericardiophrenic*, and *internal thoracic arteries*. Communications also exist, through the coronary ligament and bare area of the liver, with the hepatic arterial system. The size and origin of the inferior phrenic arteries vary greatly. Their caliber ranges from 1 to 4 mm. They may exit bilaterally (60%) from either the aorta or celiac artery, or one from the former and the other from the latter. They may emerge as a common trunk (40%), either from the aorta (20%), from the celiac artery (18%), or from the left gastric artery (2%), before branching into left and right inferior phrenic arteries.

From the trunk of the posterior branch of the inferior phrenic artery, multiple *superior suprarenal arteries* arise, which, with the *middle suprarenal artery* (from the aorta) and *inferior suprarenal artery* (from the renal or accessory renal arteries), will supply blood to the suprarenal (adrenal) gland. Another important vessel is the *recurrent esophageal branch*, which is given off by the left inferior phrenic artery shortly after it has passed posterior to the esophagus. The right inferior phrenic artery gives off several branches that supply oxygenated blood to the inferior vena cava.

From the posterior surface of the aorta, opposite the four upper lumbar vertebral bodies, arise four *lumbar arteries*, either via a common trunk or separately on each side. Because the aorta ends at the L4 level, a *fifth pair of lumbar arteries* frequently originate from the middle sacral or internal iliac arteries. The lumbar arteries curve around the vertebral bodies and pass posterior to the sympathetic trunk, psoas major, and quadratus lumborum muscles, except for the fourth lumbar segmental artery, which often traverses anterior to the latter. The right lumbar arteries travel posterior to the inferior vena cava, and L1 and L2 arteries run posterior to the cisterna chyli. Each lumbar artery gives off a long posterior branch, which, via medial, lateral, and spinal rami, supplies the skin and muscles of the back, the spinal ligaments, and the spinal cord. Leaving the lateral border of the quadratus lumborum muscle, the lumbar arteries continue between the transversus abdominis and internal abdominal oblique muscle layers. As they travel toward the rectus abdominis muscle, they release lateral cutaneous and anterior cutaneous branches and anastomose with the lower *intercostal*, *iliolumbar*, and *superior and inferior epigastric arteries* and the *ascending branch of the deep circumflex iliac artery*.



The lumbar arteries participate in an arterial circle formed by adipose capsular branches from the renal, suprarenal, and gonadal arteries.

The unpaired, visceral branches from the abdominal aorta that feed the foregut, midgut, and hindgut are the celiac, superior mesenteric, and inferior mesenteric arteries, respectively. The renal arteries exit the aorta at the level of L1 or between L1 and L2 and supply the

kidneys, suprarenal glands, and proximal ureters. The gonadal (testicular or ovarian) vessels exit the anterior surface of the aorta inferior to the renal arteries at a level varying from L1 to L3, but they may occasionally arise from a suprarenal, phrenic, superior mesenteric, lumbar, common iliac, or internal iliac artery. They may appear as a duplicated artery (17%) on one side or, less frequently, on both sides. An important abnormality

BLOOD SUPPLY OF THE ABDOMEN (Continued)

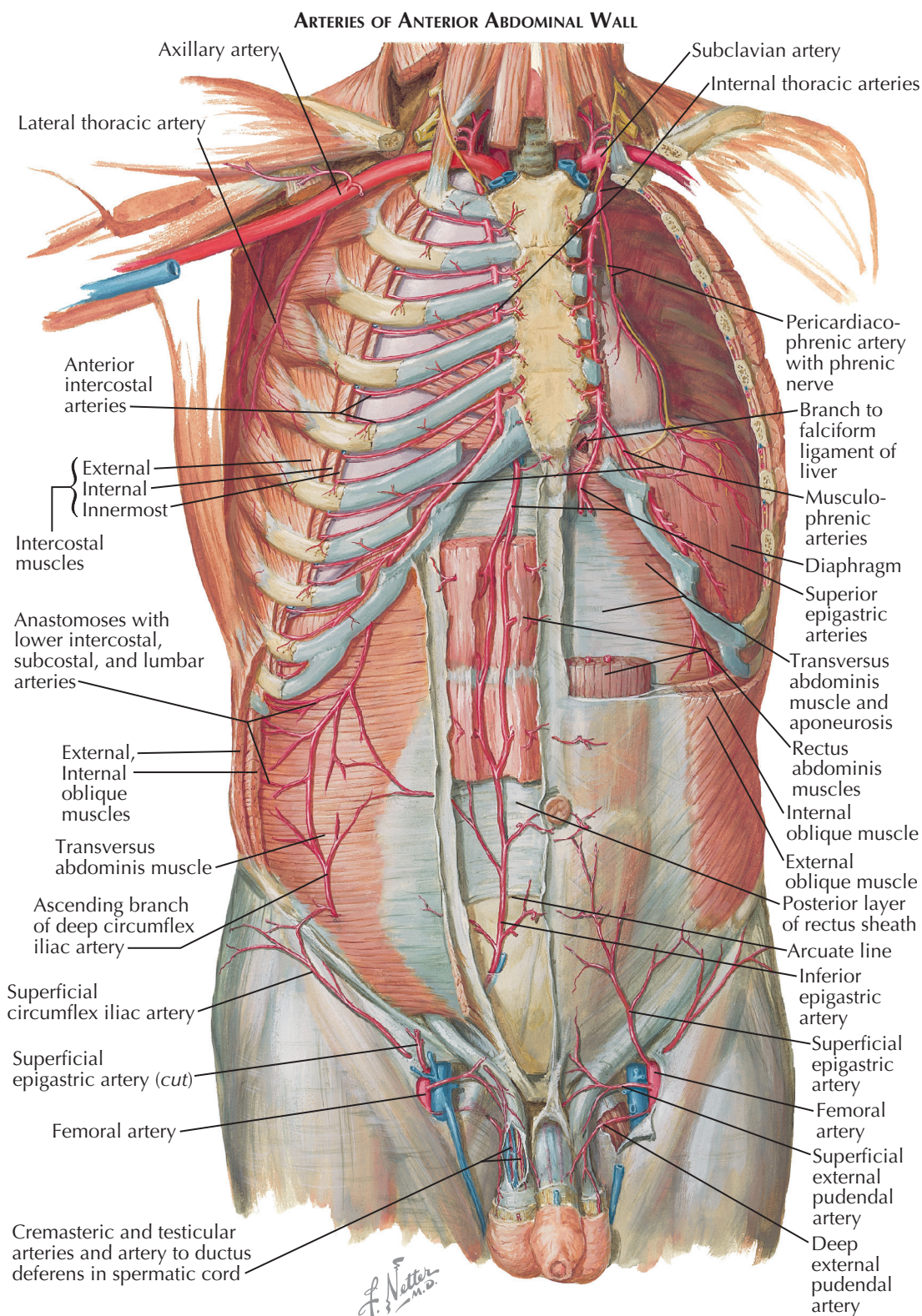
concerns an arched gonadal artery (arched testicular artery of Luschka), which originates from the aorta posterior and inferior to the renal vein but ascends to curve superiorly and descends anterior to the renal vein.

The aorta divides at the level of the lower third of the L4 vertebra into the approximately 6 mm-wide *common iliac arteries*, the lengths of which vary from 1 to 9 cm. Up to the point at which they divide into external and internal iliac arteries, the common iliac arteries have no branches, except for small, unnamed branches to the peritoneum and subperitoneal tissue.

The *superior epigastric* and *musculophrenic arteries* (both terminal branches of the internal thoracic artery) supply the anterolateral wall superiorly. The latter vessels travel inferiorly in a space posterior to the lower costal cartilages and send branches to the seventh to ninth intercostal spaces, the lower pericardium, and the superior region of the abdominal muscles. Terminating at the 10th and 11th intercostal spaces, they *anastomose* with the *intercostal* and *subcostal arteries*, with additional small connections to the *lumbar* and *deep circumflex iliac arteries*. A branch piercing the diaphragm communicates with the anterior ramus of the inferior phrenic artery. The superior epigastric artery, entering the rectus sheath posterior to the seventh costal cartilage and descending posterior to the rectus abdominis muscle, ramifies to supply this muscle and gives off a number of small cutaneous branches. It anastomoses with the inferior epigastric artery.

The main vessels that feed the inferior abdominal wall are the *inferior epigastric* and *deep circumflex iliac arteries*. Both arise from the *external iliac artery*, the former on its medial side and the latter on its lateral side just superior to the inguinal ligament. The inferior epigastric artery runs superiorly toward the umbilicus, supplying blood to the nearby peritoneum, transversalis fascia, and rectus sheath. It has several branches that supply the abdominal muscles and overlying subcutaneous tissue and skin. Typically it anastomoses heavily with the superior epigastric and lower intercostal arteries. Shortly after its origin, the inferior epigastric artery releases the *cremasteric artery* and a small *pubic artery*. The latter artery anastomoses with a branch of the obturator artery to supply structures on the posterior aspect of the pubic bone. The cremasteric artery accompanies the spermatic cord to supply the cremasteric muscle and fascia, ultimately anastomosing with the testicular artery. In the female, this artery accompanies the round ligament.

The deep circumflex iliac artery courses in a sheath formed by the union of the transversalis and iliac fasciae (or between the latter and the peritoneum) laterally and superiorly toward the anterior superior iliac spine. After piercing the transversalis fascia along the inner lip of the iliac crest, it continues to the crest's midpoint and passes through the transverse abdominal muscle to pursue a posterior course between this and the internal abdominal oblique muscle. An ascending branch,



leaving the main artery near the anterior superior iliac spine, anastomoses with the subcostal, lumbar, and lower intercostal arteries; other branches communicate with the superficial circumflex iliac, inferior epigastric, iliolumbar, and superior gluteal arteries.

The final three arteries that supply blood to the abdominal wall are branches of the *femoral artery*. The *superficial epigastric artery* passes superiorly across the inguinal ligament and courses toward the umbilicus, supplying the superficial inguinal lymph nodes as well

as the skin and the subcutaneous tissue of the medial, lower abdomen. The *superficial circumflex iliac artery* courses anterior to and parallel with the inguinal ligament (after piercing the fascia lata), providing blood to the upper thigh and lateral side of the abdomen. The *external pudendal artery* emerges through the fossa ovalis and travels medially across the spermatic cord or round ligament to supply the skin and subcutaneous tissue in the suprapubic region. One branch anastomoses with the dorsal artery of the penis or clitoris.

VENOUS DRAINAGE OF THE ABDOMEN

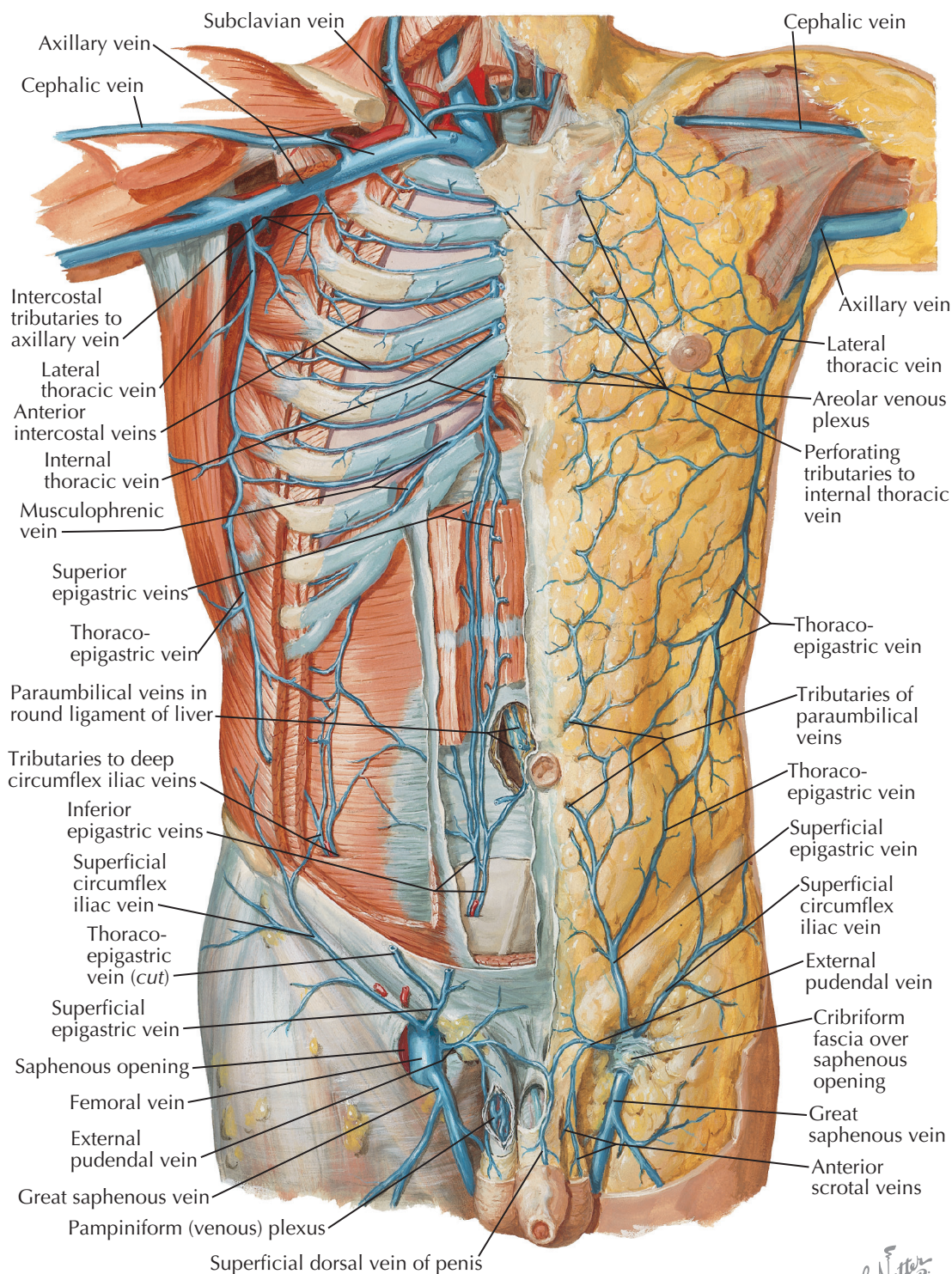
The main collecting vessels of the abdomen are the inferior vena cava and the hepatic portal vein. The hepatic portal vein drains to the liver and it originates from smaller veins that drain the alimentary tract, its associated glands, and the spleen. Here we will focus on the inferior vena cava and its tributaries, starting with the superficial veins that drain the anterolateral abdominal wall. Please note that these veins accompany the arteries of the same name, mostly in duplicate (venae comitantes) on both sides of the artery, being enwrapped in the same sheath.

The *external pudendal vein*, aside from branches originating from the region above the symphysis pubis, receives the venous blood from the external genitalia (*superficial dorsal vein of the penis or clitoris* and the subcutaneous veins of the *scrotum or labia majora*), and joins, in many instances, the *great saphenous vein* or the *femoral vein*. The *superficial epigastric* and *superficial circumflex iliac veins*, draining the medial and lateral parts of the lower abdominal wall, respectively, pass superficial to the inguinal ligament and, piercing the cribriform fascia, enter the femoral vein (in other instances, the great saphenous vein). In the body's midaxillary line the superficial veins of the upper and lower halves of the trunk communicate through the *thoracoepigastric veins*, which unite in the axilla with the *lateral thoracic veins*, each a branch of an *axillary vein*. This system of anastomosis plays an important role in the event of an obstruction of the superior or inferior vena cava. The thoracoepigastric veins receive numerous tributaries from the surrounding superficial fascia as well as veins emerging from the lateral aspect of the mammary gland.

Another collateral venous circulation of clinical significance comes about through the superficial supraumbilical and infraumbilical veins, which, by means of five or six *paraumbilical veins* arising from the integument and the musculoaponeurotic structures or the abdominal wall, course within the ligamentum teres and enter the left branch of the portal vein. When portal venous pressure rises in liver cirrhosis, the paraumbilical veins establish collaterals with the superior and inferior epigastric and thoracoepigastric veins, and become enlarged and tortuous, assuming a radial pattern known as the *caput medusae* (head of Medusa).

The two deeper veins that drain the anterolateral abdominal wall are the *inferior epigastric* and *deep circumflex iliac veins*, both of which enter the external iliac vein (the continuation of the femoral vein) after having drained the same regions supplied by the corresponding arteries. This network of anastomoses, including the musculophrenic and superior epigastric veins, likewise conforms to the location of the arteries. The *external iliac vein*, beginning posterior to the inguinal ligaments, courses with its homonymous artery superiorly along the brim of the lesser pelvis to unite with the internal iliac vein anterior to the sacroiliac joint to form the common iliac vein.

VEINS OF ANTERIOR ABDOMINAL WALL



The *internal iliac vein* collects the blood from all pelvic structures, except the upper part of the rectum and the sigmoid colon, which drain to the portal system via the inferior mesenteric vein, and the ovaries and testes, which reach the inferior vena cava directly via the gonadal veins. Starting near the superior part of the greater sciatic foramen and ascending over the piriform and psoas major muscles, the internal iliac vein receives the *superior and inferior gluteal, internal pudendal, obturator, lateral sacral, middle rectal, and superior vesical veins*.

Many of these vessels have their origins in a rich venous plexus, such as the *pudendal, urethrovesical, and uterovaginal plexuses*.

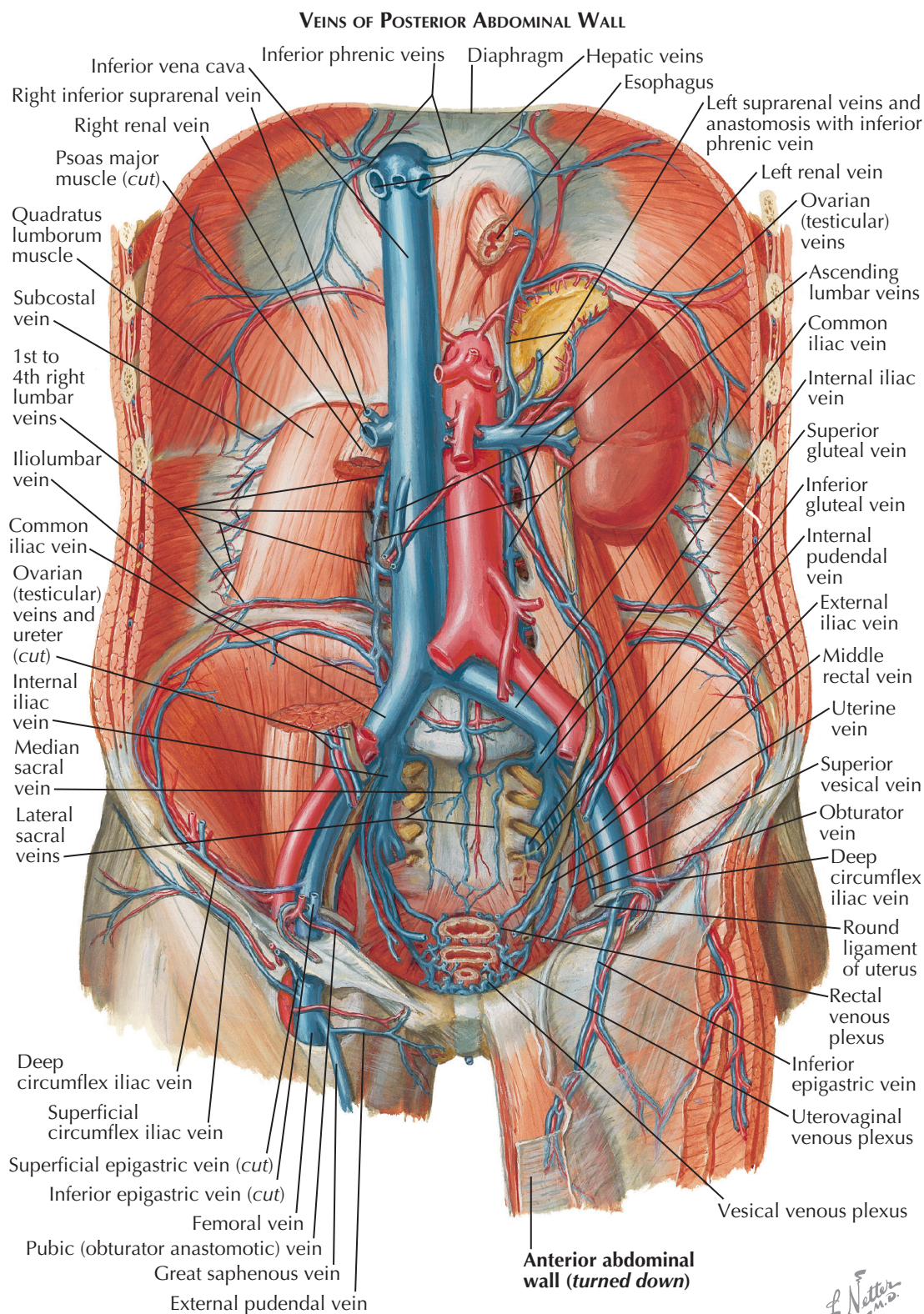
The *common iliac veins* continue along the course of the external iliac veins in a median direction until the left vein meets the right vein, marking the starting point of the inferior vena cava. The left common iliac vein, often somewhat longer than its right counterpart, receives the middle sacral vein when this unpaired vessel does not enter (as it does frequently) the angle of

VENOUS DRAINAGE OF THE ABDOMEN (Continued)

the two iliac veins. Both common iliac veins receive the *iliolumbar veins* and, in some instances, the lateral sacral veins, if the latter have not entered the internal iliac vein or have not joined the fifth lumbar vein.

The *inferior vena cava* commences at the right of L5, ascends along the aorta anterior to the vertebral column, and continues posterior to the liver in a groove between the bare area and the caudal lobe. Immediately after the inferior vena cava receives the three hepatic veins (draining the liver), the inferior vena cava leaves the abdomen through the diaphragm's *caval hiatus* in the central tendon. Because the caval hiatus lies superior to the aortic hiatus and the union of the two common iliac veins is inferior to the aortic bifurcation, the inferior vena cava in the abdomen is about 7 to 8 cm longer than the abdominal aorta. The first veins to enter the inferior vena cava are the *lumbar veins*. The lowest (fifth) lumbar vein empties to the iliolumbar vein, whereas the upper four lumbar veins, lying on the bodies of the vertebrae and accompanying the arteries, drain into the posterior wall of the inferior vena cava but may drain to the azygos or hemiazygos veins. The connections that the lumbar veins make with the renal, suprarenal, gonadal, deep circumflex, iliac, and other abdominal veins are manifold. The most important concerns the longitudinal anastomosis effected through the *ascending lumbar veins*. These veins, beginning in the pelvis as a continuation of the lateral sacral veins, ascend deep in the sulcus between the tendinous origins of the psoas major muscle and the bodies and transverse processes of the vertebrae; after receiving branches from the lumbar veins, the right ascending lumbar vein drains into the azygos and the left into the hemiazygos, or sometimes into the left renal vein. Posteriorly, the ascending lumbar veins make numerous connections with the valveless veins of the vertebral venous system and thus bring the caval system into relationship with the veins of the spine, spinal cord, dura mater, vertebrae, and brain. These relationships provide an explanation for the spread of infections, tumors, and thrombi from the pelvis, abdomen, or thorax into the central nervous system, or bones of the skull and spine.

The right *gonadal (testicular or ovarian) vein* enters the inferior vena cava superior to the lumbar veins, whereas the left gonadal vein usually merges with the left renal vein, or possibly the suprarenal vein, or one of the lumbar veins. The testicular veins, starting from the pampiniform plexus in the spermatic cord, ascend along the ductus deferens, pass through the inguinal canal, and, following the artery, course superiorly on the psoas



major muscle. The ovarian veins, derived from the uterovaginal and ovarian plexuses, take a similar course.

The large *renal veins* lie anterior to the corresponding arteries and show much less variation than the renal arteries. The right renal vein rarely receives tributaries, whereas on the left side, supernumerary veins such as the left gonadal and suprarenal veins typically join the vessel. The right *suprarenal vein* usually terminates with a direct connection with the inferior vena cava

and, occasionally, right renal vein. The left suprarenal vein typically drains into the left renal or inferior phrenic vein.

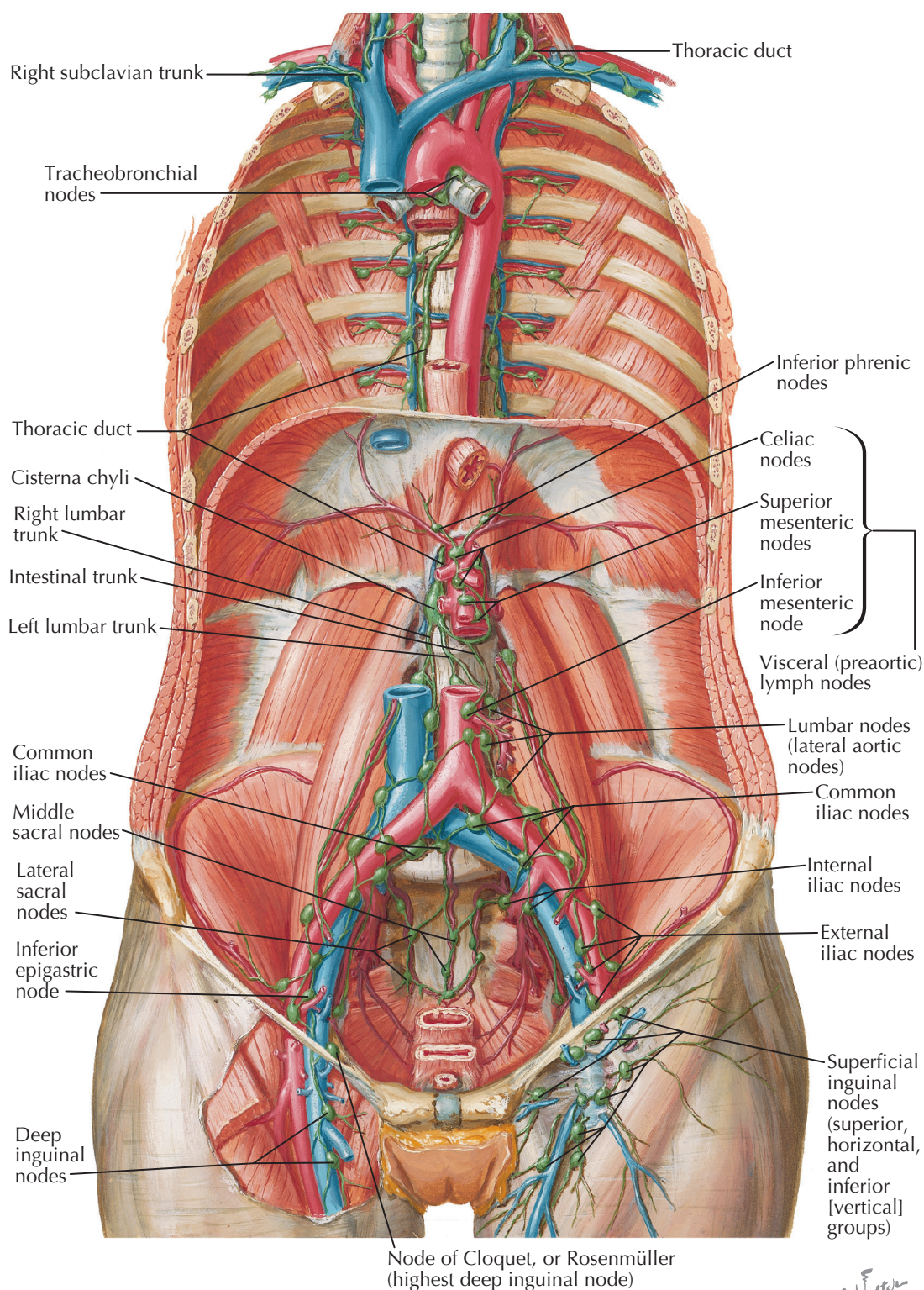
Superior to the hepatic veins are the uppermost tributaries of the inferior vena cava, the *inferior phrenic veins*, which generally follow the course of the homonymous arteries. The left one may join the left renal vein separately or via a common trunk with the left suprarenal vein (5%).

LYMPH DRAINAGE OF THE ABDOMEN

The major lymphatic channels of the posterior abdominal wall are essentially located along the large blood vessels. Thus the *external iliac lymph vessels*, interrupted by *nodes* of the same name, course with the external iliac arteries and veins. Entering the pelvis posterior to the inguinal ligament about midway between the anterior superior spine of the ilium and symphysis pubis, these vessels receive lymph from the *deep* (and thereby also *superficial*) *inguinal lymph nodes*, through which pass the lymphatic drainage of the lower extremities, the inferior parts of the anterolateral abdominal wall, and the perineum (including the external genitalia and anal region). The *internal iliac lymph vessels* run, interrupted by the *internal iliac nodes*, with the artery and vein of the same name and drain the larger part of the organs and wall of the true pelvis, whereas the remaining part of this region releases lymph through the presacral lymphatics. The external and internal iliac lymphatics join to form *common iliac lymph vessels and nodes* of the same name. Common iliac lymph vessels also receive input from the presacral lymphatics with their *lateral and middle sacral nodes*. The latter are situated in the retrorectal connective tissue over the anterior surface of the sacrum. In the region of the aortic bifurcation, the common iliac lymph vessels proceed superiorly along the lateral walls of the aorta to become the *right and left lumbar trunks*. These trunks and the interposed *lateral aortic lymph nodes* receive afferents from the kidney and the *visceral (preaortic) lymph nodes*. The extremely large area of drainage that the lumbar trunks serve includes, thus, the walls and organs of the lower abdomen as well as of the lower extremities.

Both lumbar trunks unite in the region of the aortic hiatus, anterior to the vertebral column (in the majority of cases), at the level of the upper third of L1 and the intervertebral disc between vertebrae T12 and L1, to form the beginning of the *thoracic duct*. In about 50% of individuals, the thoracic duct starts with a distinctive, elongated, saccular dilatation (≈ 1 to 1.5 cm in diameter and 5 to 7 cm in length), the *cisterna chyli*. Its three main roots are the single *intestinal trunk* and the two lumbar trunks; however, two smaller tributaries coming from a cranial direction and descending through the aortic hiatus of the diaphragm also join the cisterna chyli.

The thoracic duct passes first to the right across the posterior surface of the aorta, through the aortic hiatus of the diaphragm into the mediastinum, ascending between the aorta and the azygos vein, anterior to the lower thoracic vertebrae and right intercostal arteries. On reaching the level of the fifth thoracic vertebra, it courses posterior to the esophagus to the left side of the spinal column, where it runs for a short distance to the right of the aorta and then crosses posterior to the aortic arch to continue its ascent. Opposite the third



thoracic vertebra, the thoracic duct draws away from the spinal column in an anterior direction and proceeds between the left common carotid artery and the left subclavian artery, through the superior thoracic aperture, and into the left supraclavicular fossa. Here it arches superior to the subclavian artery and opens either into the angle at which the left jugular and left subclavian veins join to form the left brachiocephalic vein or, less often, into one of the two veins forming

this angle. At its point of entry into the veins, the thoracic duct does not always form a single entity but sometimes divides into a triangular structure composed of two or more branches. During its passage through the thorax, the thoracic duct is joined by vessels connecting with the posterior parietal, tracheobronchial, and posterior mediastinal lymph nodes, as well as smaller lymph vessels draining the thoracic wall and thoracic organs.

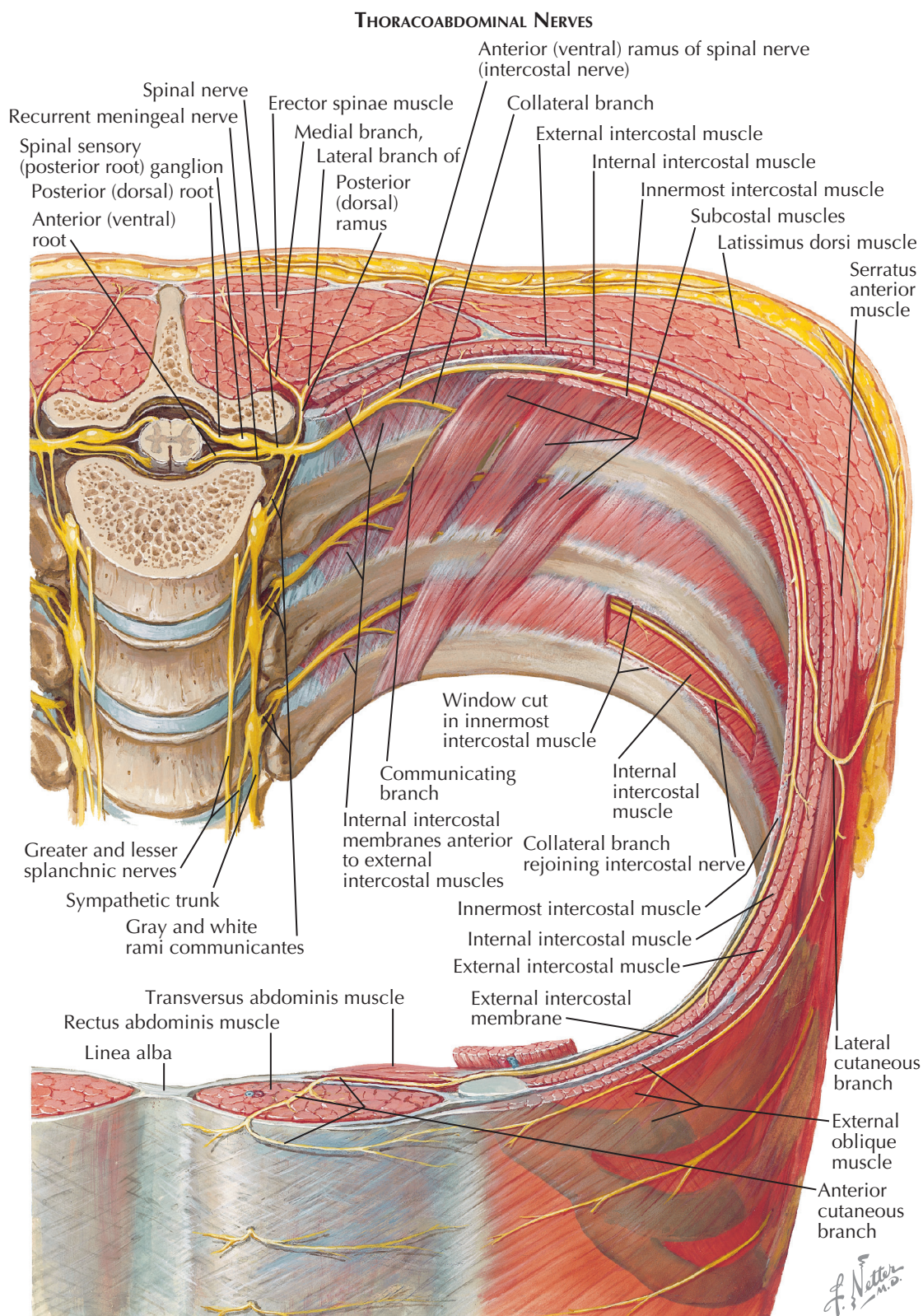
INNERVATION OF ABDOMEN AND PERINEUM

The segmentally arranged nerves are attached to the sides of the spinal cord by a series of *anterior (ventral)* and *posterior (dorsal)* roots. An anterior and posterior root at each spinal segment unite to form the *spinal nerve*, which emerges through the corresponding intervertebral foramen. The anterior roots contain axons from the motor nerve cells in the anterior horn of the spinal cord and the posterior roots contain the axons projecting from the pseudounipolar sensory cells located in the *posterior (dorsal) root ganglia* (spinal sensory ganglia).

The spinal nerve only exists for a short span before dividing into *anterior* and *posterior rami*, each of which carries both motor and sensory axons to their target tissues. Before splitting into rami, each of the spinal nerves gives off a small *recurrent meningeal branch* that is sensory to the nearby spinal dura mater and intervertebral foramen. After emerging from the intervertebral foramen, each spinal nerve receives a branch or branches (*gray rami communicantes*) from an adjacent ganglion of the *sympathetic trunk*, which contains postganglionic sympathetic axons originating from the cells of that ganglion. Of the first thoracic through the first two or, occasionally, three lumbar anterior rami, each contributes a branch or branches (*white rami communicantes*), which contain preganglionic sympathetic fibers to the corresponding sympathetic ganglia.

In general, the posterior rami are smaller than the anterior rami and do not unite to form plexuses. They divide into *medial* and *lateral branches* that supply the muscles and skin of the back. The anterior rami supply the anterolateral aspects of the trunk as well as the limbs. In the cervical, lumbar, sacral, and coccygeal regions, the anterior rami converge to form plexuses, but in the thoracic region, they maintain their segmental character and each runs separately and independently to the site or structure it innervates.

The thoracic anterior rami, the *intercostal nerves*, are distributed chiefly to the anterolateral walls of the thorax and abdomen. They are 12 in number on each side, but only 11 are truly intercostal. The 12th pair lie below the last ribs and are termed *subcostal nerves*. The upper six pairs of intercostal nerves are limited in their supply to the thoracic body wall, although the first and second intercostal nerves also contribute to the brachial plexus, the innervation of the upper limbs. The fourth



nerve innervates the skin at the level of the nipple. The lower five pairs of intercostal nerves and the subcostal nerves supply the thoracic and abdominal body wall and also contribute fibers to the diaphragm.

Typically, the 7th to 11th intercostal nerves course anteriorly along the thoracic wall below the corresponding rib and intercostal vessels. Posteriorly, the nerve lies between the pleura and the *posterior intercostal membrane* and passes between the *internal* and *innermost intercostal muscles*. Each nerve gives off a *collateral branch* and a

lateral cutaneous branch. The former, separating from the primary ramus only a few centimeters away from the vertebrae, inclines inferiorly from the parent nerve, runs along the lower border of the intercostal space, and ends anteriorly as a small cutaneous nerve. The lateral cutaneous branch accompanies the main intercostal nerve as far as the midaxillary line before piercing the intercostal muscles and dividing into anterior and posterior branches, which are mainly cutaneous in distribution. The intercostal nerves supply intercostal, subcostal, and

NERVES OF ANTERIOR ABDOMINAL WALL

INNERVATION OF ABDOMEN AND PERINEUM (Continued)

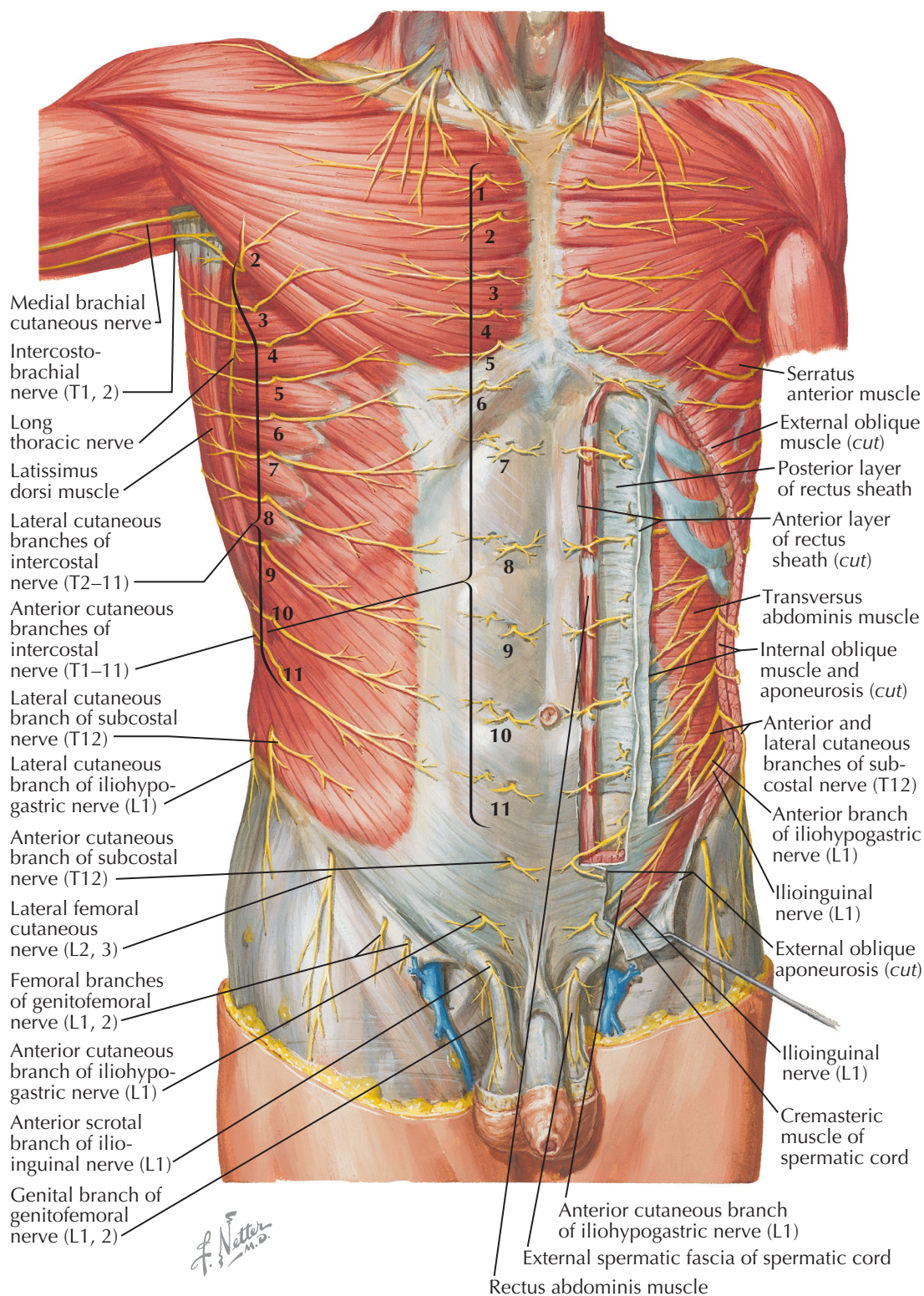
transverse thoracic muscles. The lower five or six intercostal nerves also supply sensory axons to the peripheral parts of the diaphragm.

The lower five intercostal nerves and the subcostal nerves pass posterior to the *costal cartilages* and enter the abdominal wall to supply the *external and internal abdominal oblique*, *transversus abdominis*, and *rectus abdominis* muscles and end as *anterior abdominal cutaneous branches*. The 10th nerve serves the dermatome at the level of the umbilicus. The lateral cutaneous branch of the subcostal nerve (T12) pierces the internal and external oblique abdominal muscles and descends over the iliac crest to assist in supplying the skin over the upper lateral part of the thigh.

The anterior rami of the lower spinal nerves (five lumbar, five sacral, and one coccygeal) divide and reunite in a plexiform fashion to form the *lumbar*, *sacral*, and *coccygeal plexuses*. They are interconnected as described above with the *sympathetic trunks* via *rami communicantes*.

The *lumbar plexus* is formed by the anterior rami of the first three lumbar nerves and the greater part of the fourth lumbar nerve, along with a contribution from the subcostal nerve. It is situated anterior to the lumbar vertebral transverse processes and is embedded in the posterior part of the *psoas major* muscle, which needs to be dissected to make the plexus accessible. The most common course and distribution of the components of the plexus and its relationship are described and illustrated here, but it should be kept in mind that variations of the lumbar plexus are frequent.

The first lumbar nerve, after receiving a twig from the subcostal nerve, splits into an upper branch and a smaller lower branch. The former divides into the *iliohypogastric* and *ilioinguinal nerves*, and the latter unites with a twig of the second lumbar nerve to form the *genitofemoral nerve*. The rest of the second lumbar nerve, the third, and that part of the fourth which contributes to this plexus, each divide also into anterior and posterior sections, which combine to constitute the *obturator* and *femoral nerves*, respectively. The *accessory obturator nerve*, when present, is formed by branches from the anterior divisions of the third and fourth nerves, whereas the *lateral femoral cutaneous nerve* evolves by the fusion of small offshoots from the posterior divisions of the second and third lumbar nerves.



Muscular branches from the subcostal and upper four lumbar nerves supply the *quadratus lumborum muscle*, and those of the first and second reach the *psoas major* and *psoas minor muscles*. The *psoas major* muscles are further innervated by branches from the third and, sometimes, fourth lumbar nerves, which also supply the *iliacus muscles*.

The *iliohypogastric* and *ilioinguinal nerves* resemble the thoracic nerves in their course and distribution, being analogous, respectively, to the main trunk and the

collateral branch of an intercostal nerve. The former nerve gives off a *lateral branch*, which crosses the iliac crest a short distance posterior to the corresponding branch of the subcostal nerve, both nerves supplying skin of the superior lateral part of the thigh. Continuing anteriorly, the *anterior branch* of the *iliohypogastric nerve* sends filaments to the transverse and oblique abdominal muscles, pierces the *external oblique aponeurosis* about 3 cm superior to the superficial inguinal ring, and terminates innervating the skin just superior to the pubis.

INNERVATION OF ABDOMEN AND PERINEUM (Continued)

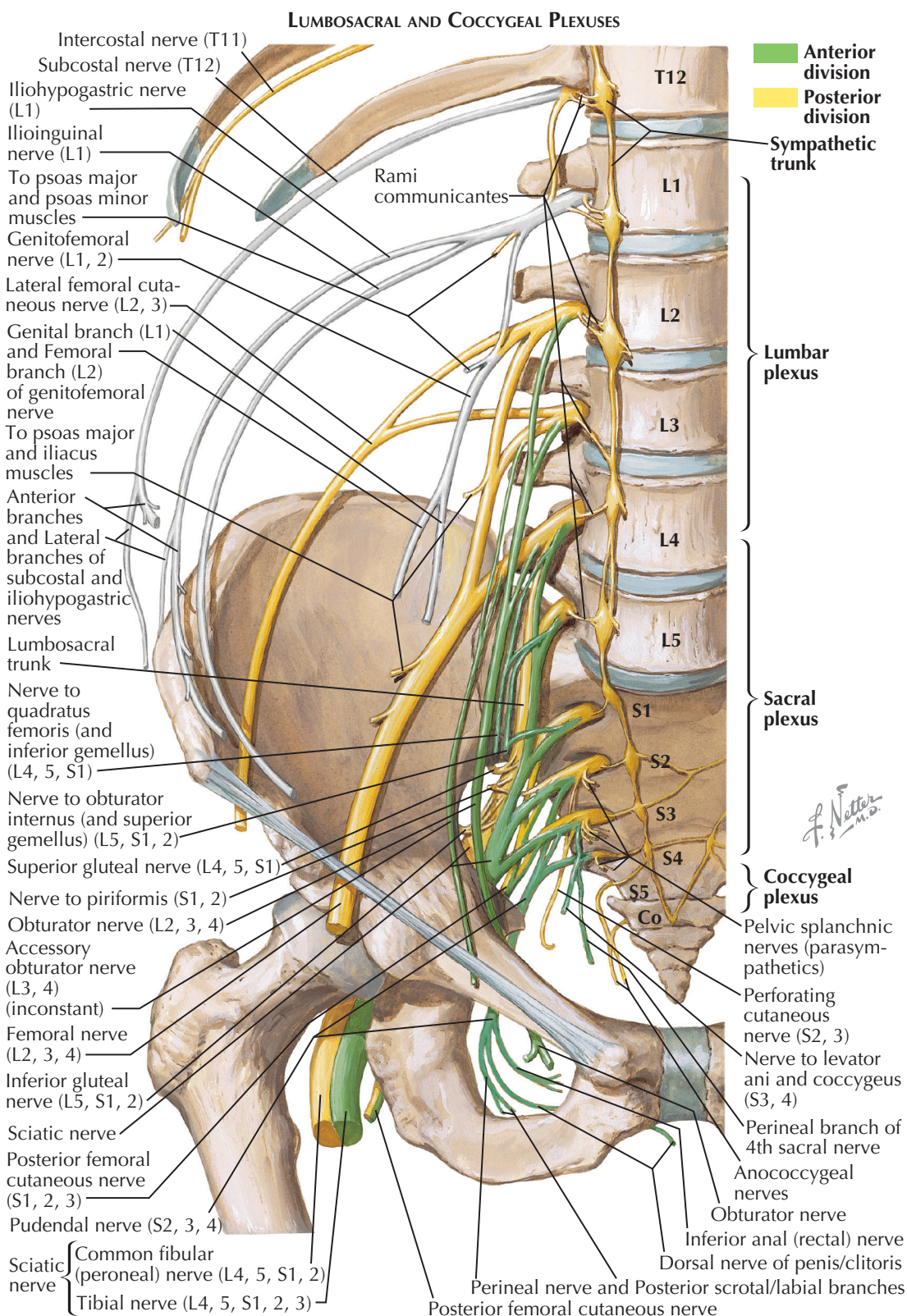
The ilioinguinal nerve supplies filaments to the adjacent muscles and, after piercing the same muscles as the iliohypogastric nerve, enters the inguinal canal, runs deep to the spermatic cord, and emerges through the superficial inguinal ring to supply the superior medial side of the thigh, the root of the penis, and the anterior part of the scrotum in the male, and the mons pubis and labium majora in the female.

The *genitofemoral nerve*, after emerging from the lumbar plexus, passes through the psoas major muscle and descends on its anterior surface, deep to the peritoneum, to divide into the *genital* and *femoral branches* at about the level of the fifth lumbar vertebra. The former branch enters the inguinal canal through the deep inguinal ring, innervates the cremaster muscle, and contributes some twigs to the skin of the scrotum, or the labium majora of the female. The femoral branch runs lateral to the external iliac and femoral arteries, passes posterior to the inguinal ligament, and, after piercing the anterior layer of the femoral sheath and the fascia lata, ramifies in the superficial tissues and skin over the femoral triangle. The genitofemoral nerve and its branches carry many of the efferent and afferent fibers to and from the common iliac, external iliac, and femoral arteries.

Other branches of the lumbar plexus (e.g., the *femoral nerve*), except for muscular rami to the quadratus lumborum, psoas major, and iliacus muscles, are distributed to the lower limb and, consequently, are not discussed in this volume.

The anterior rami of the sacral and coccygeal nerves, which, in contrast to the lumbar nerves, diminish in size as they progress inferiorly, divide and reunite to contribute to the *sacral* and *coccygeal plexuses*. These lie on the posterior wall of the pelvis, posterior to the ureters, internal iliac vessels, and intestinal coils, and anterior to the piriformis and coccygeus muscles. The inferior and smaller part of the fourth lumbar nerve unites with the anterior ramus of the fifth lumbar nerve as the *lumbosacral trunk*, which, together with the anterior rami of the first three and the upper part of the fourth sacral nerves, constitutes the sacral plexus. The lower part of the fourth sacral joins the fifth sacral and coccygeal nerves to form the small coccygeal plexus.

Each nerve entering into the composition of these two plexuses receives postganglionic sympathetic fibers by way of one or more gray rami communicantes from an adjacent ganglion of the sympathetic trunk. Pregang-



lionic parasympathetic fibers originate in the second to fourth sacral levels of the spinal cord; they emerge with the second, third, and fourth sacral nerves and leave thereafter as pelvic splanchnic nerves.

The *sacral plexus*, by convergence and fusion of its roots, develops into a flattened band, from which many branches arise, before the large *sciatic nerve* passes through the greater sciatic foramen inferior to the

piriformis muscle. This large nerve consists of a *tibial section* and a *common fibular section*, which usually remain fused until about the lower third of the thigh, but which may occasionally be separated at their points of origin or may divide before the nerve leaves the pelvis. The nerve of the sacral plexus splits into anterior and posterior divisions, which, in some individuals, unite again to produce the nerves. Most branches of the sacral

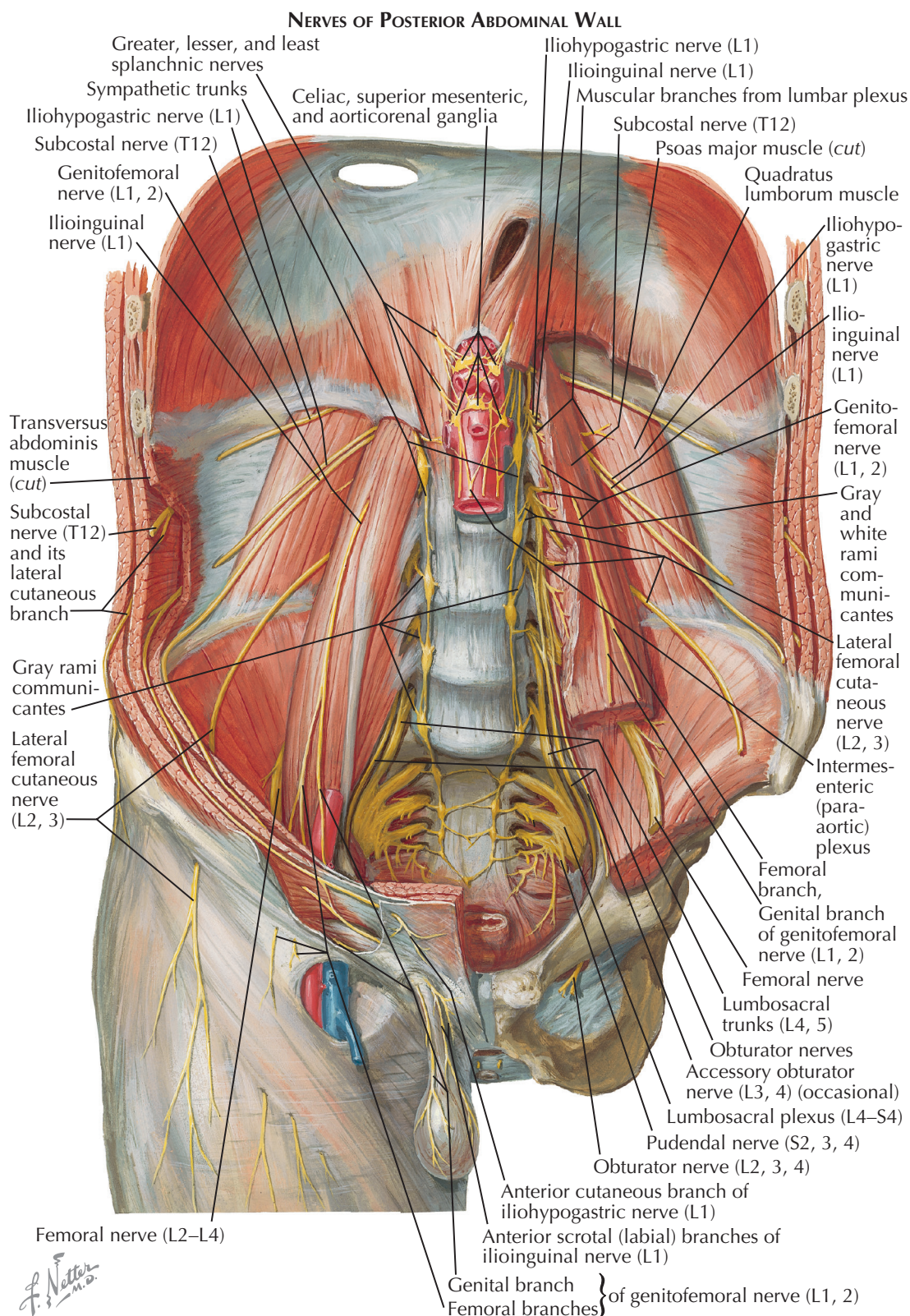
INNERVATION OF ABDOMEN AND PERINEUM (Continued)

plexus supply the lower limb and will be discussed in the volume addressing the musculoskeletal system. Others are distributed in the pelvic and perineal regions.

The *nerve to the piriformis*, levator ani, and coccygeus muscles pierce the anterior or pelvic surfaces of these muscles. The nerve to the *obturator internus muscle* (not to be confused with the obturator nerve) leaves the pelvis through the greater sciatic foramen inferior to the piriformis muscle, crosses the ischial spine lateral to the pudendal nerve and internal pudendal vessels, reenters the pelvis through the lesser sciatic foramen, and sinks into the pelvic surface of the obturator internus muscle.

The *pudendal nerve* passes between the piriformis and coccygeus muscles, leaves the pelvis through the greater sciatic foramen, alongside the sciatic nerve, crosses posteroinferior to the ischial spine (medial to the internal pudendal artery), and accompanies that vessel through the lesser sciatic foramen into the pudendal canal on the obturator internus fascia. As the nerve enters the canal, it gives off the inferior rectal nerve and shortly thereafter terminates by splitting into the perineal nerve and the dorsal nerve of the penis or clitoris, respectively.

The inferior rectal nerve perforates the medial wall of the pudendal canal, crosses the ischioanal fossa obliquely with the inferior rectal vessels, and divides into branches that are the main supply of the external anal sphincter, the lining of the lower part of the anal canal, and the skin around the anus. Its branches communicate with the perineal branches of the posterior femoral cutaneous, fourth sacral, and perforating cutaneous nerves and the *perineal nerve*, which is the larger terminal branch of the pudendal nerve. This latter nerve runs anteriorly in the pudendal canal inferior to the internal pudendal artery, projecting toward the posterior border of the urogenital diaphragm, near which it divides into superficial and deep branches. The superficial one divides into *medial* and *lateral posterior scrotal (or labial) nerves*, which spread over the skin of the scrotum or labia majora, communicating with the perineal branch of the posterior femoral cutaneous nerve. The deep branches supply the anterior parts of the external anal sphincter, the superficial and deep transverse perineal, *bulbospongiosus*, and *ischiocavernosus muscles*, as well as the sphincter urethrae (and, in a subsidiary fashion, the levator ani). A twig, termed the nerve of the bulb, arises from the branch to the bulbo-



spongiosus muscle and is distributed to the erectile tissue of the corpus spongiosum and the mucous membrane of the urethra.

The *dorsal nerve of the penis* accompanies the internal pudendal artery in its course through the *deep transverse perineal muscle* and passes anterior to the pubic arch under cover of the ischiocavernosus muscle and corpus cavernosum penis. Passing through a gap between the inferior fascia and the apex of the urogenital diaphragm,

the nerve comes to lie alongside the dorsal artery of the penis and continues as far as the glans and the prepuce. In the female the dorsal nerve of the clitoris is smaller, but its distribution is similar.

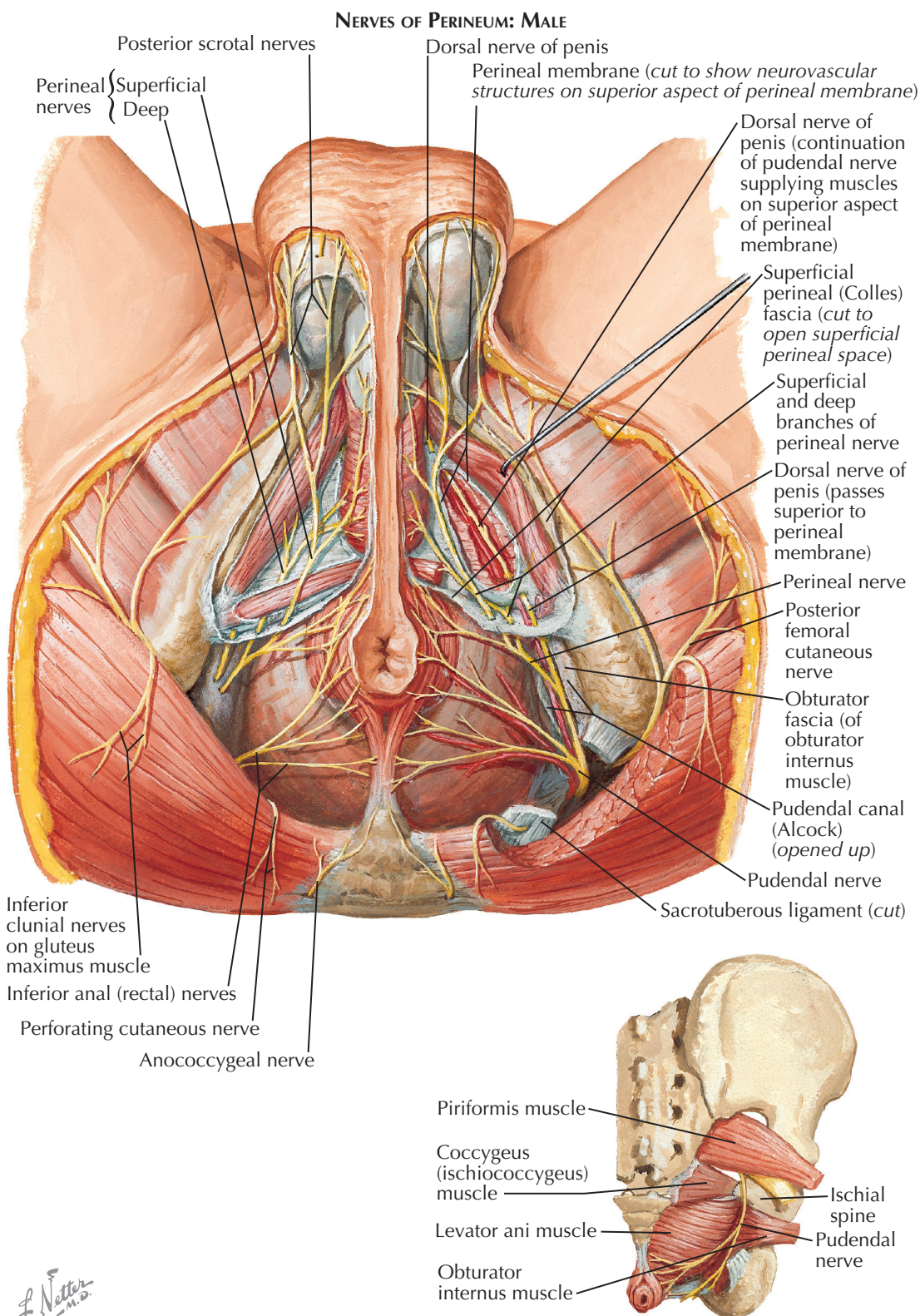
The *posterior femoral cutaneous nerve*, besides innervating the skin of the posterior thigh, gives off a gluteal branch, the inferior cluneal nerve, supplying the skin area over the lower part of the gluteus maximus and, in the same region, a perineal branch that curves

INNERVATION OF ABDOMEN AND PERINEUM (Continued)

anteriorly and medially inferior to the ischial tuberosity to the skin and fasciae of the perineum, scrotum, and root of the penis. The distribution is similar in the female, to the perineum, labia majora, and root of the clitoris. Its terminal twigs communicate with the inferior rectal and perineal branches of the pudendal and terminal filaments of the ilioinguinal nerves. The *perforating cutaneous nerve* pierces the sacrotuberous ligament and turns around the lower margin of the gluteus maximus to become cutaneous a short distance lateral to the coccyx. Its origin and distribution, however, are not constant. It may be joined or replaced by branches from the pudendal nerve, posterior femoral cutaneous nerve, or *perineal branch of the fourth sacral nerve*, arising from a loop between the third and fourth sacral nerves. This branch reaches the posterior angle of the ischioanal fossa by perforating the coccygeus muscle and then divides into some twigs that run anteriorly to assist the innervation of the external anal sphincter and others that ramify in the overlying skin and fascia.

The *coccygeal plexus* is formed by the union of the inferior part of the anterior ramus of the fourth sacral nerve with those of the fifth sacral and coccygeal nerves. The plexus is small and really consists of two loops on the pelvic surface of the coccygeus and the levator ani muscles. It gives off fine twigs to the parts adjacent to both these structures, as well as the delicate anococcygeal nerves that pierce the sacrotuberous ligament and supply the skin in the vicinity of the coccyx.

Having discussed the nerves supplying the wall of the abdominal cavity, the lumbar, sacral, and coccygeal plexuses, and the nerves they release to innervate part of the abdominal viscera and floor (pelvis as well as perineum) of the abdominal cavity, it remains to consider the innervation of the diaphragm, which forms the roof of the abdominal cavity. The diaphragm is supplied by the phrenic and lower intercostal nerves. Each phrenic nerve contains both motor and sensory fibers; the latter convey afferent impulses from the pleura, pericardium, peritoneum, and other structures. The motor fibers are the axons of the phrenic nucleus in the third, fourth, and fifth cervical cord segments. If one phrenic nerve is destroyed, complete muscular atrophy



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occurs in the corresponding half of the diaphragm, so it is presumed the intercostal nerve supply must be sensory.

The phrenic nerves are distributed mainly on the inferior surface of the diaphragm. The right pierces the central tendon just lateral to the caval hiatus and divides into anterior and posterior branches that supply all the muscle fibers on the same side, including the crural fibers on the right side of the esophagus and those

arising from the arcuate ligaments. The left nerve pierces the diaphragm about 3 cm anterior to the central tendon and thereafter supplies the left half of the muscle, including the fibers of the right crus lying to the left of the esophageal hiatus. The phrenic branches communicate with autonomic fibers from the celiac plexus accompanying the inferior phrenic arteries. On the right side a small ganglion marks one of these interconnections.

OVERVIEW OF THE DIGESTIVE SYSTEM

The digestive system is by far the largest and most complex of the internal organ systems. The interplay of its multiple organs, its intrinsic hormonal and neural systems, and its intricate and interacting physiologic functions are among the most fascinating aspects of human physiology. Although the primary function of each organ is to interact effectively with other organs to provide nutrition to the rest of the body, several organs also have distinct metabolic functions that are of vital importance.

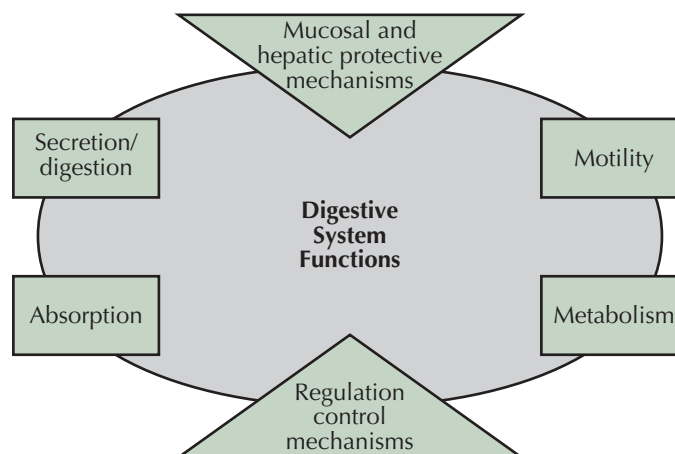
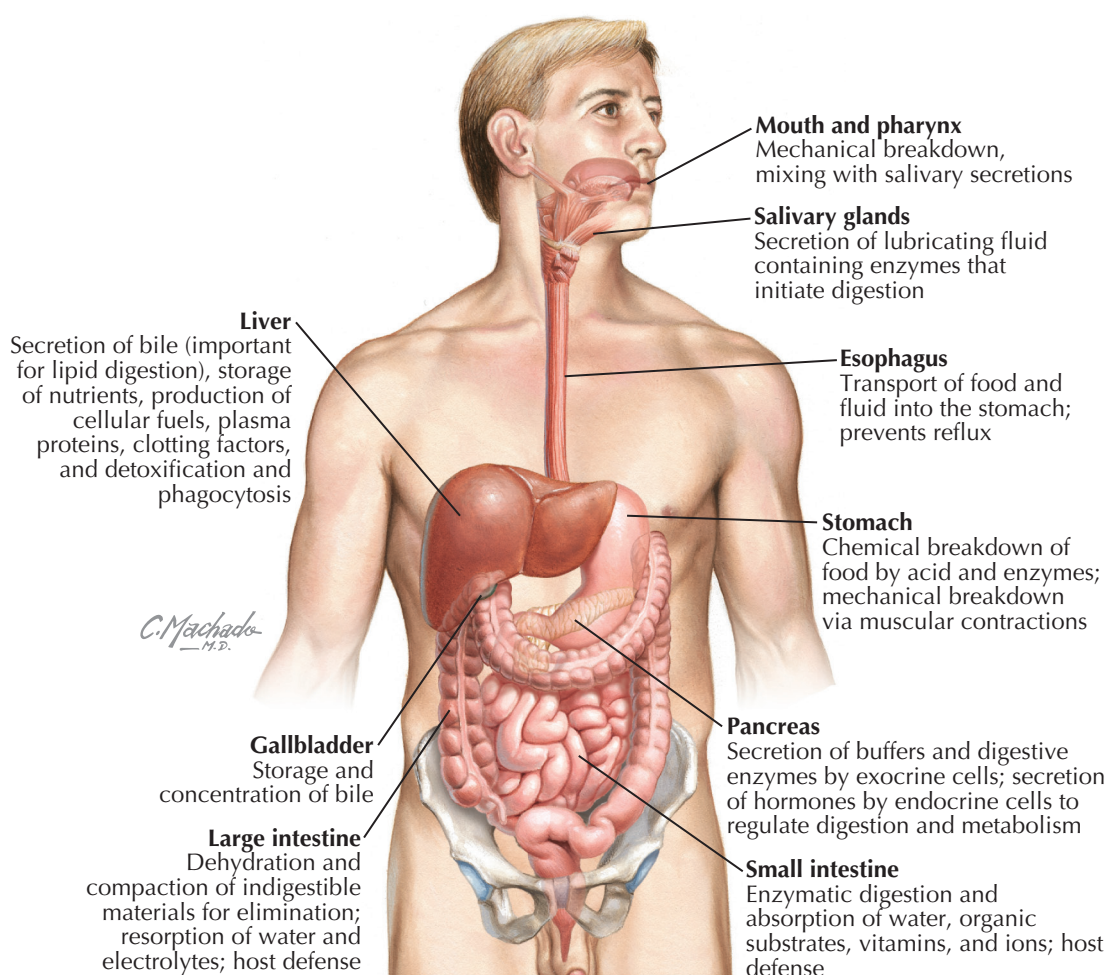
Appreciating the role of each organ begins with asking how the four essential functions of each are regulated and how immune and other defense mechanisms are protecting that organ. The wall of each luminal organ is composed of three layers of distinctly functioning muscle groups responsible for moving nutrients and fluids from the mouth until they are discharged from the anus. The electromechanical coupling mechanisms responsible for motility by which this occurs are surprisingly distinct for each organ. An electrical syncytium regulates these contractions with rhythmic depolarizations called *slow waves* and contraction-inducing depolarizations resulting in *action potentials*. Action potentials are similar throughout the luminal organs, but slow wave activities in the stomach, duodenum, and colon vary in frequency.

All luminal and solid gastrointestinal organs are involved with secretions that facilitate digestion and mucosal protection, leading to nutrient absorption. In contrast, the esophagus has the least secretion and no absorption and the liver and pancreas are involved with secretion only and not motility or absorption.

The liver is the most important and largest metabolic organ. Metabolic functions are also provided by proteins synthesized by the small bowel and by hormones secreted by the stomach, pancreas, and small bowel.

Regulation of each organ is achieved with a complex interaction between the extrinsic autonomic nervous system, intrinsic or enteric nervous system, and hormones secreted both within and outside the digestive system. The hormones of the digestive system were the first endocrine substances to be discovered. The small intestine is clearly the largest of all endocrine organs. Each of the neurotransmitters identified in the enteric nervous system of the digestive system is also found in the brain. Again, many were first discovered in the gut.

The lumen of each of the digestive organs is filled with potentially lethal chemicals and microorganisms. Distinct, organ-specific, highly effective defense mechanisms exist in each organ to prevent disease. The gut's microbiome develops shortly after birth and grows to a point of containing 10 trillion organisms, or nearly 10 times as many cells as the rest of the body! Other important defense mechanisms with unique actions in



each organ include motility, intrinsic secretion, lubrication with fluid and mucus, and frequent cell turnover.

When these protective systems break down or become impaired, disease begins. Disorders of the digestive tract are the second most common reason, after upper respiratory tract disorders, that patients seek help from a primary care physician or are absent from work or school. In a typical year, approximately 60% of individuals experience some digestive system dysfunction, whether acute or chronic. Common digestive disorders affecting 15% to 20% of the U.S. population include functional bowel disturbances, gastroesophageal reflux disease, peptic ulcer disease, hepatitis, gallbladder stones, and infectious diseases of the stomach and intestines. These and other gastrointesti-

nal disorders account for 25% of all hospitalizations. Of all primary neoplasms leading to death, one third originate in digestive system organs. Cancers of the digestive system continue to be the most common cause of all cancer deaths. Lung cancer is overall the most common type of cancer, but cancers of the colon, pancreas, liver, stomach, and esophagus are among the 10 commonest cancers.

One of the most fascinating aspects of the pathophysiology of the digestive system is the marked difference in the prevalence of disorders in men and women. Eosinophilic esophagitis, esophageal adenocarcinoma, and hepatocellular carcinoma are much more common in men, and irritable bowel syndrome and gallstone disease are much more common in women.

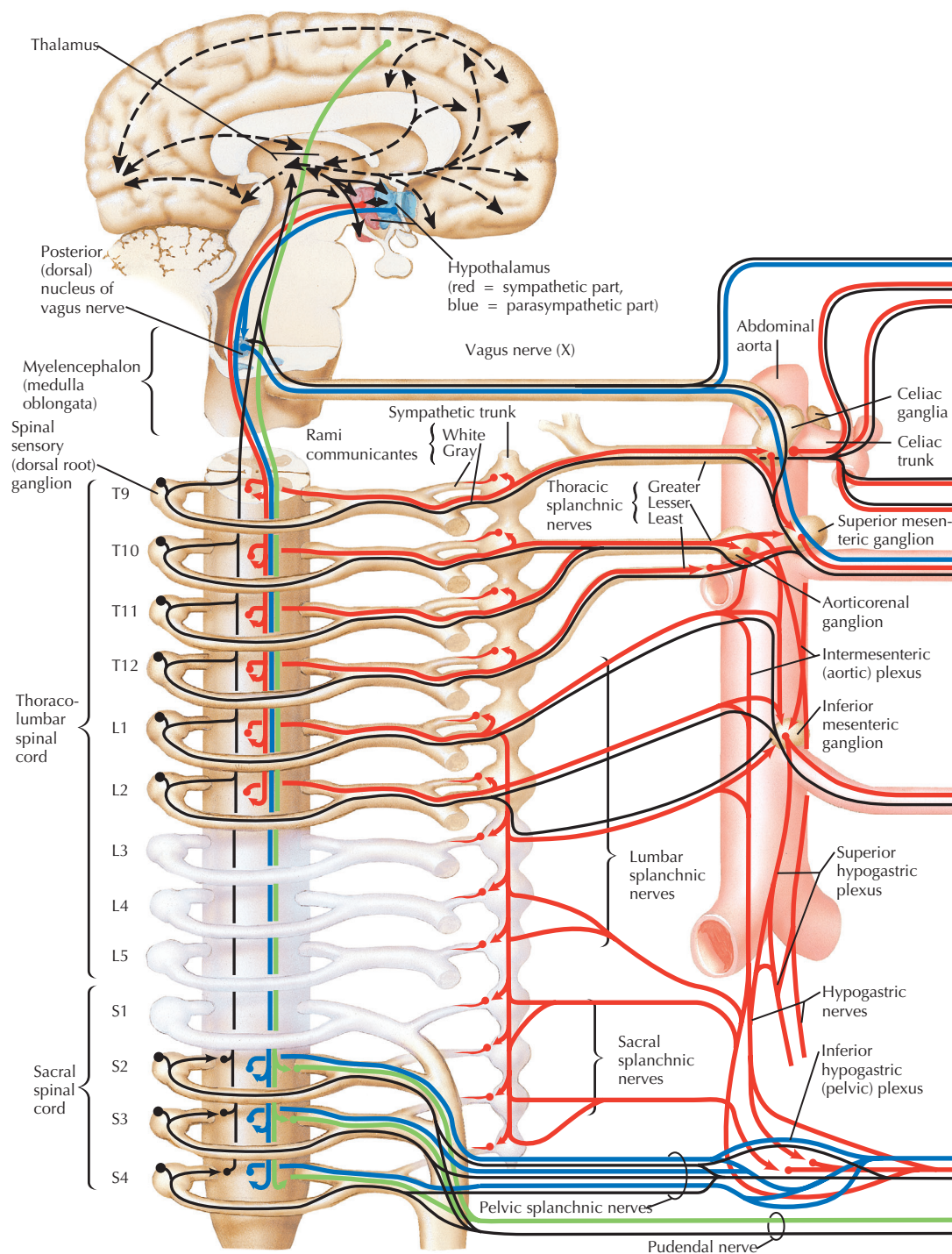
OVERVIEW OF CONTROL MECHANISMS

The digestive system is controlled by a fascinatingly complex interaction between extrinsic and intrinsic hormones, the extrinsic and intrinsic nervous systems, and a unique electrical control system. Recent increases in our understanding of the neural and hormonal regulatory systems have shown that many of the neurotransmitters crucial to functioning of the CNS are also found in the gut. In fact, many were first identified in the gut and then shown to also exist in other organs, including the brain.

ELECTRICAL CONTROL SYSTEM

Effective, well-organized contractions throughout the tubular digestive system are of critical importance to digestion and absorption in the mixing and propelling of intraluminal contents. As in other muscles, contractions result from cell membrane depolarizations that are recorded as action potentials. These membrane changes are responsible for effective electromechanical coupling by opening calcium channels that stimulate actin-myosin interactions. To cause coordinated, circular contractions that will effectively move luminal contents, these depolarizations must occur around the lumen. This is made possible by an electrical syncytium that preferentially creates simultaneous depolarizations around the lumen. Depolarizations occur in a rhythmic fashion from electrical pacemaker potentials created by the interstitial cells of Cajal. These paced depolarizations, which facilitate coordinated contractions around the lumen, are known as *slow waves*. They are not seen in the esophagus or fundus of the stomach but first develop in the upper body of the stomach at a frequency of three cycles per minute. Gastric paced slow waves progress down the stomach and end at the pyloric sphincter. In the small intestine, the rate of slow waves created by the pacemakers is higher in the duodenum (17 to 18 cycles per minute) than the jejunum and even slower in the ileum (14 to 16 cycles per minute). This gradient of slow wave frequency contributes to the proximal to distal movement of luminal contents. The progressive movement of slow waves from the proximal to the distal lumen also permits peristalsis to occur in a caudal direction. Slow wave frequencies in the colon are more complex and less uniform but are generally thought to occur at three to six cycles per minute.

Slow waves result in forceful mixing or peristaltic contractions only in the presence of stimuli that result in further cell membrane depolarizations that create an action potential. The presence of an electrical syncytium favoring circular depolarizations around the lumen permits a circular contraction to be produced from the stimulus that creates the action potential. Thus, slow waves control spatial relationships and directions of movement of gastric and intestinal luminal contractions that were created by action potentials that created electrical responses. Action potential stimulation may originate from extrinsic hormones, extrinsic neurotransmitters, intrinsic hormones, or intrinsic neurotransmitters.



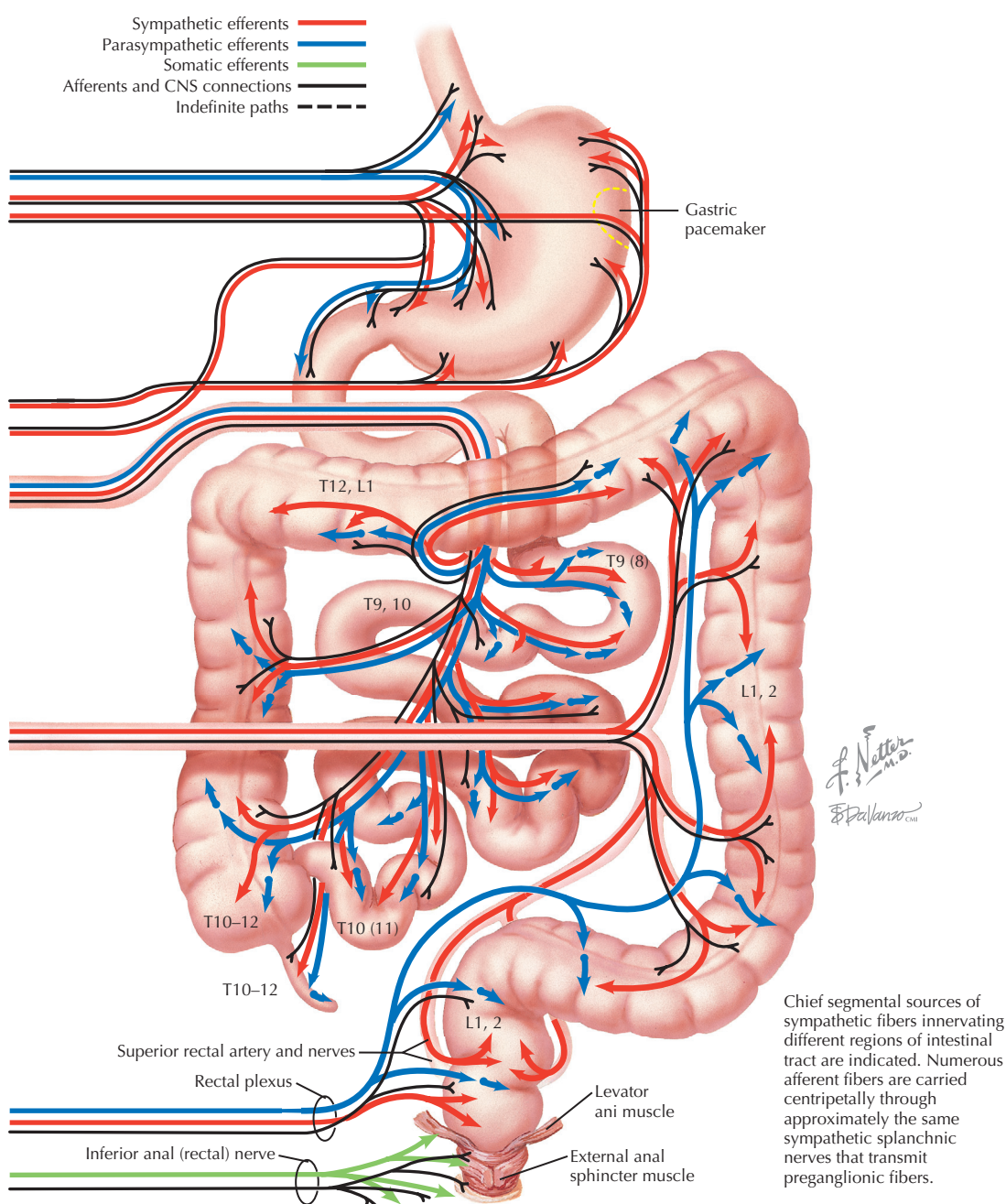
EXTRINSIC ENDOCRINE SYSTEM

Extrinsic hormones that have a broad influence on all organ systems also affect the gut; they include thyroid hormones, adrenocorticotropic hormone, corticosteroids, mineralocorticoids, corticotropin-releasing factor, and leptin. Leptin is a CNS hormone that has a primary role in influencing digestion by reducing food intake and modulating the metabolism of nutrients. The complex role of hormones in the regulation of appetite and satiety is discussed in [Plates 1-56 and 1-57](#). Both deficiencies and excesses of thyroid hormones may lead to gut malfunction. Patients with hypothyroidism often complain of constipation and loss of appetite. If the disorder progresses to myxedema, motility dysfunction can develop throughout the digestive system, with impaired peristalsis and contractility.

Corticotropin-releasing hormone has a major role in the physiologic response to stress. Levels of this hypothalamic hormone increase during actual stressful events, as when a person is facing a traumatic situation, but also during events that are not inherently stressful but are perceived as stressful. The latter situation leads to challenges in diagnosing and managing functional bowel disorders.

EXTRINSIC NERVOUS SYSTEM

The previous theory that digestive system functions are primarily regulated by the autonomic nervous system and, thus, the CNS is overly simplistic. The influence of the autonomic nervous system is mediated by a balance of the stimulatory effects of the parasympathetic nervous system and inhibitory effects of



OVERVIEW OF CONTROL MECHANISMS (Continued)

adrenergic neurons in the sympathetic nervous system. Only 10% to 20% of vagal nerves are efferent, far too few to control the many complex responses of the seven digestive organs, much less all the other visceral organs. Direct input to gut functions by the autonomic nervous system is important, but the system serves as the primary control system only in the striated muscle regions of the pharynx and upper esophagus via cranial nerves and in the rectum and anal sphincter via sacral and pelvic nerves. Sympathetic nerves reach the gut to mediate blood flow and help to “shut down” the gut during the fight-or-flight response via the intermedio-

lateral column to splanchnic nerves originating from T2 to L3. These then innervate the gut via nerves whose bodies are in the celiac, superior mesenteric, or inferior mesenteric ganglia.

The autonomic nervous system primarily serves to modify local gut reflexes, but it also plays a critical role in a variety of gut reflexes and in communicating afferent information to the brain. Medications that inhibit cholinergic neurons are a cornerstone of treatment of spastic disorders of the entire gastrointestinal tract. Anticholinergics are also widely used to reduce oral secretions during endoscopy, oral surgery, or anesthesia. The importance of vagal stimulation of gastric secretions explains why surgical selective vagotomy is sometimes used to manage complex ulcer disease.

The sympathetic nervous system’s fight-or-flight reflex leads to diarrhea and contributes to functional

disorders in patients plagued by anxiety and hypervigilance. Increased sympathetic tone during stress associated with trauma or sepsis is needed to maintain the blood pressure and circulation but often results in a severe reduction in gut blood flow known as a *mesenteric steal*. Decreased blood flow reduces metabolic support for the intrinsic protective mechanisms of the stomach, resulting in unopposed acid injury and severe, at times even hemorrhagic, gastritis.

Enteric Nervous System

The amazing expansion of our understanding of the intrinsic or enteric nervous system, both experimentally and clinically, indicates that the complexity of the system is similar to that of the CNS. The predominance of the enteric nervous system can be best appreciated by observing the successful function of liver, pancreatic, small bowel, and even colon transplants in the absence of neural input from the CNS. The enteric nervous system is so crucial for digestion that a separate section is dedicated to its description (see [Plate 1-46](#)).

INTRINSIC ENDOCRINE SYSTEM

The field of endocrinology was conceived when the first hormone, secretin, a major hormone in the digestive system, was discovered in 1914. Our knowledge of the digestive system’s intrinsic endocrine system’s transmitters, functions, and molecular processing has grown exponentially since then. Gut hormones stimulate the coordination of widely diverse functions in each of the digestive organs to work in concert to digest and absorb food. Gut hormones achieve this by modifying secretion, absorption, motility, and metabolism.

Gut hormones alter metabolism not only in the digestive system but throughout the body. Insulin released from pancreatic islet cells is the best example of this important role of gut hormones. Other gut hormones that have a major role in modifying metabolism include glucagon, cholecystokinin, peptide YY, insulin-like growth factor 1, and ghrelin. Ghrelin is a hormone released from the stomach and proximal small bowel that increases food intake.

Many gut hormones influence gastrointestinal motility. Cholecystokinin and secretin coordinate the response to food intake by altering gastric emptying, duodenal contractions, gallbladder contractions, and contractions of the sphincter of Oddi (relaxed) and pyloric sphincter (contractions). Perhaps the most fascinating physiologic event of the digestive system is coordinated emptying of the upper digestive tract during fasting. This occurs when forceful contractions of phase III of the *interdigestive motor complex*, known as the *intestinal housekeeper*, are initiated by the hormone motilin.

Well-defined clinical syndromes have been recognized that are due to neuroendocrine tumors. Advances in technology have led to the recognition that such hormone-secreting tumors are more common than previously appreciated. These important hormone regulators of gut function and the disorders for which they are known to be responsible are discussed in [Plate 1-49](#).

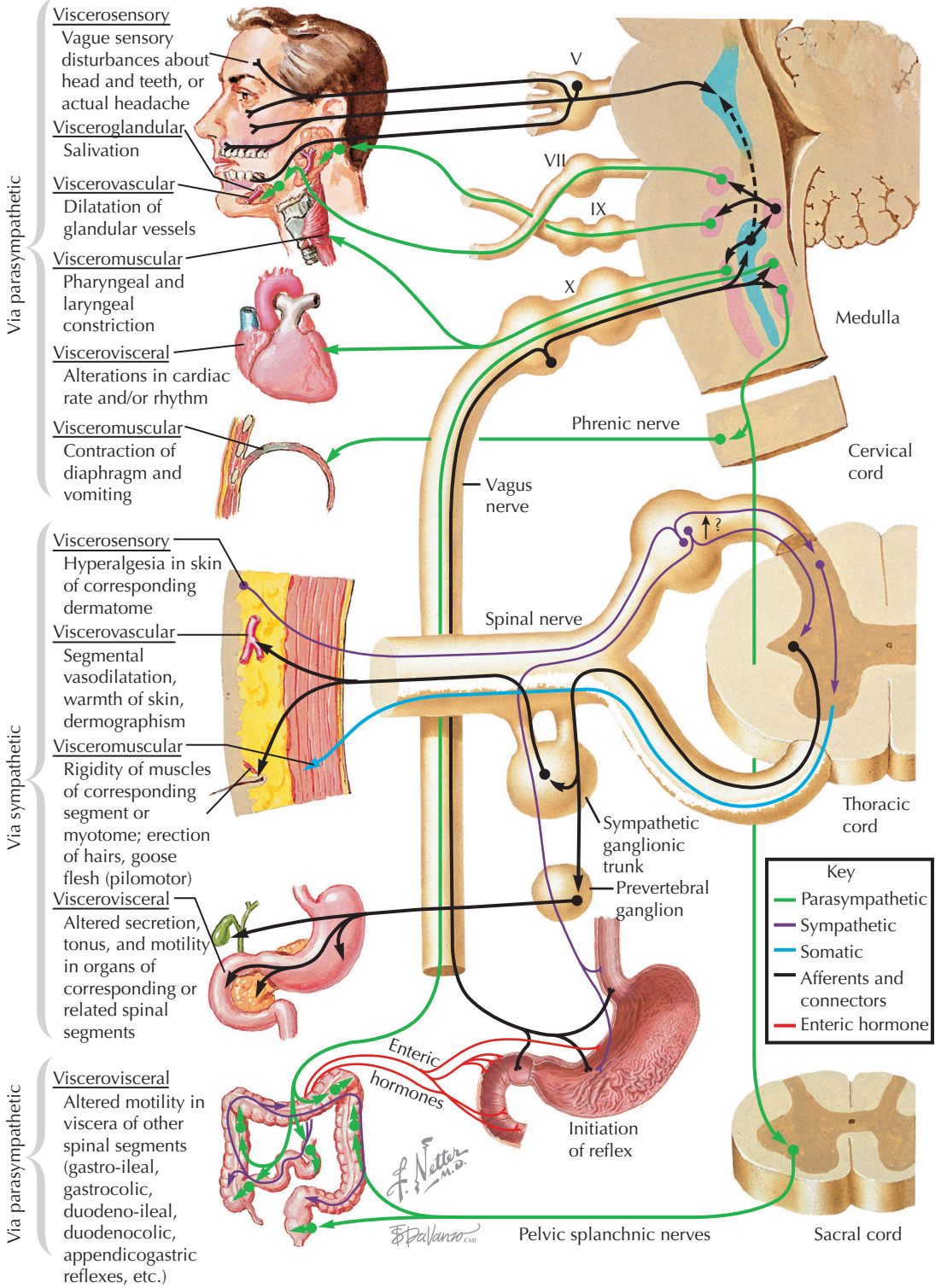
It can readily be appreciated that the digestive system’s seven organs are regulated by a complex interaction of the extrinsic nervous system and extrinsic hormonal system which modulates the more reflexive “hard-wired” reflexes of the enteric nervous system and intrinsic hormonal system. The clinician’s challenge is to determine which of these mechanisms is at play in causing a patient’s symptoms and disease.

BRAIN-GUT INTERACTIONS AND VISCERAL REFLEXES

The similarities in neurotransmitters in the gut and CNS further stimulated our understanding of the interactions of the brain and gut. Since the time of Pavlov and Komarov and their colleagues, reflexes between the brain and gut and within the gut have been shown to control much of normal physiology and pathophysiology. Visceral reflexes explain a number of clinical signs, many of which are controlled by complex interactions mediated by spinal or CNS pathways. Such vagal or sympathetic reflexes initiate patterned behaviors that often involve multiple organs. Such reflexive responses stimulated by extrinsic neurons are then mediated locally by enteric neural pathways or intrinsic hormones.

One of the most important and well-studied brain-gut reflexes is the one associated with the control of gastric and pancreatic secretion. Sights, smells, sounds, and even the anticipation of food serve as external cues that can stimulate vagally mediated reflexes. Perhaps the best known is the reflexive increase in acid secretion that prepares the stomach to begin digestion. These reflexes are both instinctive and learned. Although it is initiated as an autonomic nervous system vagal reflex, the release of acid is ultimately mediated by complex interactions of histamine released from enteroendocrine cells and the systemic release of gastrin. Excess stress is known to cause gastric upset. Such stress is often attributed to “nerves” and dismissed, but it may be an important cause of disease, including peptic ulcers, as described by Cushing. For example, the incidence of perforating gastric and duodenal ulcers increased markedly in England during the bombings of World War II.

Another very important visceral reflex is the *gastrocolic reflex*. This normal physiologic response of postprandial emptying of the colon occurs gradually as a meal is consumed and colonic contractility increases progressively over the next 30 to 60 minutes. The reflex is initiated by specific receptors in the duodenum that respond to the intake of fatty acids but not liquid alone or nonessential amino acids. Patients who suffer from irritable bowel syndrome have an exaggerated gastrocolic reflex. Colonic contractility is not only more forceful but begins sooner than normal. Spastic contractions occur shortly after a meal is ingested and often peak in intensity before the meal is complete, causing diarrhea, cramping pain, and/or bloating. In this centrally initiated reflex, local serotonergic neurons in the myenteric plexus stimulate propulsive and spastic contractions that at one time may lead to constipation and at another, diarrhea. Afferent impulses from the hypercontractile and often distended sigmoid colon initiate reflexes to the CNS (e.g., headache, a strange feeling in the head), to the bronchial tree (difficulty in breathing), to the stomach (epigastric distress, indigestion), and to the abdominal skin (intolerance of constricting garments).



The afferent limb of *viscerosomatic reflexes* originates from gut viscera and then affects other visceral and somatic structures; it may involve sympathetic or parasympathetic nerves. The efferent limb is usually via parasympathetic nerves. The viscerosensory reflexes result from shared afferent pathways where C fibers in the dorsal horn that are not myelinated from visceral organs come along with somatic afferents in the dorsal horn or spinal column. They explain the phenomena of “referred pain” and of “skin hyperalgesia,” which, in the case of sympathetic reflexes, occurs in skin areas (dermatomes) innervated by the same spinal segment from which the nerve supply of the diseased viscus is derived.

Unusual and often dangerous viscerosomatic or viscerovisceral reflexes are commonly encountered. Gastrointestinal disorders leading to vasovagal reflexes often lead to syncope in the setting of severe abdominal pain, extremes of nausea, exposure to particularly noxious substances, and severe diarrhea. In such settings, visceral “brain-gut” stimuli initiate vagally mediated hypotension, bradycardia, and diaphoresis. *Swallowing syncope*, a related reflex, occurs when a patient experiences an esophageal spasm, irritation, or distention that leads to vagally induced arrhythmias or bradycardia and syncope. Gastroesophageal reflux can rarely lead to a similar reflex.

ENTERIC NERVOUS SYSTEM

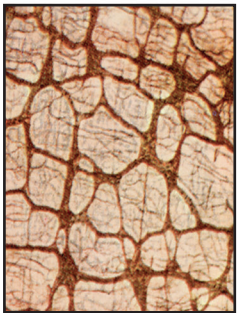
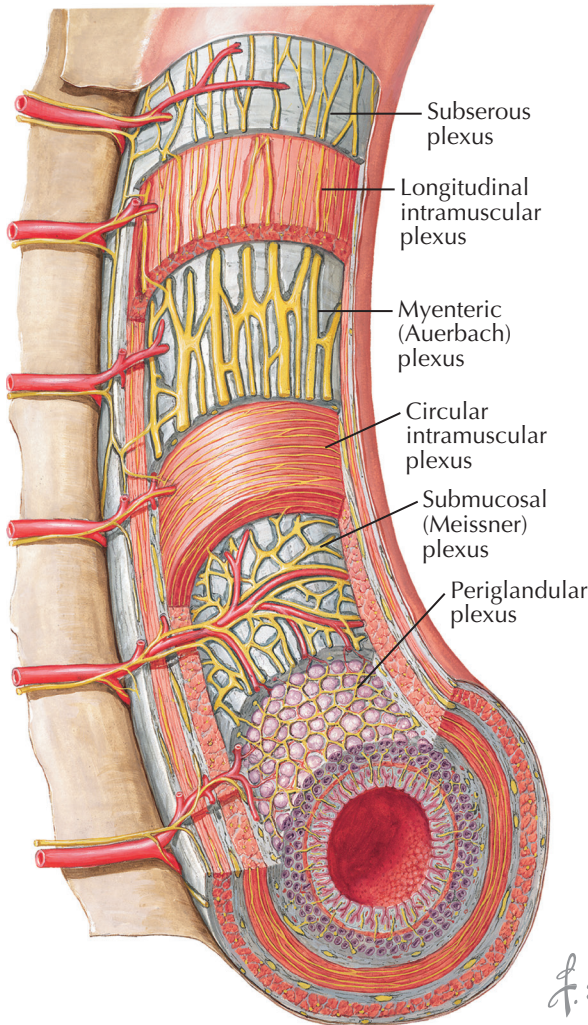
The digestive system's enteric nervous system is by far the largest neural network outside of the CNS and contains more neurons than the spinal column. The variety of neurotransmitters is similar to that in the CNS. The complexity with which these transmitters interact is fascinating and intricate. This system provides the local "hard wiring" for all local gut reflexes, most notably peristalsis. Local responses are modulated by input from the other regulatory systems (extrinsic hormones, intrinsic hormones, parasympathetic and sympathetic nerves from the autonomic nervous system, and other enteric nerves).

The bodies of neurons in the enteric nervous system are located in two layers in the gut, the *Auerbach submucosal plexus* and the *Meissner myenteric plexus*. The Auerbach plexus is located on the luminal side of the circular muscle and has sensory neurons, effector neurons, and interneurons. The simplest description of its function is that its neurons serve primarily to integrate events and conditions in the lumen with the motility functions of the muscularis mucosa and the secretory and vascular functions of the submucosa. It is important to add, however, that reflexes have been identified from the submucosal nerves to the myenteric nerves that mediate peristalsis as well as to sensory sites in the dorsal root ganglia and mesenteric ganglia. For example, light mucosal stimulation alters the peristaltic reflex via enteric nerves in the mucosa to the submucosal ganglia and to extramural ganglia in the mesentery and paraspinal ganglia.

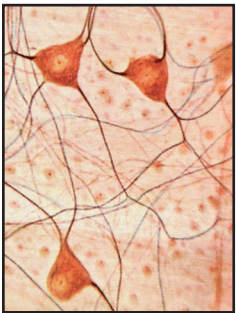
It is similarly reasonable to view the myenteric plexus as having the primary function of integrating all local reflexes, including local contractions and peristalsis, as well as the blood flow needed to perform these functions. For example, although most motor neurons are very short, interneurons containing serotonin travel several centimeters to integrate the peristaltic reflex.

The neurotransmitters in the two intrinsic plexuses are incredible in number and complexity. Enteric neurons are characterized by their morphology and neurotransmitter content. Over 30 neuropeptides have been identified and sequenced. These transmitters are grouped in families based on similarities in amino acid sequences. Although an encyclopedic summary is inappropriate for this chapter, a brief listing of well-defined neurotransmitter families found in the enteric nervous system of the digestive system is shown. Regrettably, the names initially assigned to these transmitters often had little to do with the primary functions that they were later found to perform. Furthermore, the list of functions that are influenced by each transmitter belies any effort at simplification. An anatomic factor that prevents an oversimplification of the role of these transmitters is the demonstration that a single neuron may contain more than one neurotransmitter. Colocalization of neurotransmitters occurs across different classes of transmitters, including peptidergic and nonpeptide transmitters, most notably nitric oxide. The incredibly complex, specific influence these nerves have on functions has been further demonstrated by the fact that in response to various stimuli, there may be selective release of colocalized transmitters from a single neuron.

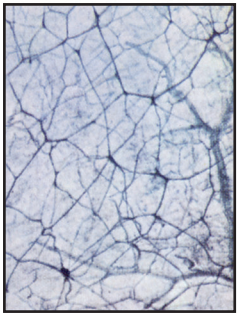
Characterization of transmitters as having specific functions risks oversimplification because the transmitters may have different effects depending on the cell of origin. Some common patterns have been noted, however. The tachykinin-neurokinin family of pep-



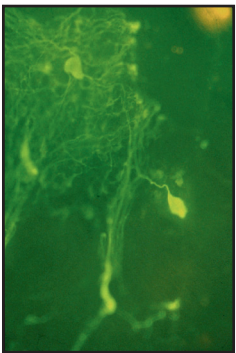
Myenteric plexus (guinea pig, Champy-Coujard, osmic stain, × 20)



Multipolar neurons, type II, in myenteric plexus (cat, Bielschowsky, silver stain, × 200)



Submucosal plexus (guinea pig, stained by Golgi impregnation, × 20)



Human myenteric plexus with VIP immunoreactive neurons

Hormone	Cell type and location
EPGF Epidermal growth factor	Enteric neurons
Gastrin-cholecystokinin Gastrin CCK	G cells in gastric antrum I cells in proximal small bowel
Ghrelin Motilin	M cells in proximal small intestine
Growth factors Transforming growth factor	
Insulin Insulin-like growth factor	B cells in pancreatic islets
Pancreatic polypeptide Peptide YY Neuropeptide Y Substance P	L cells in ileum Sympathetic neurons Enteric neurons

Hormone	Cell type and location
Secretin-glucagon Secretin GLP-1&2	S cells in proximal small bowel L cells in small intestine and B cells of pancreatic islets
VIP Glucagon GHRH PACAP	Enteric neurons A cells in pancreatic islets Enteric neurons and pancreatic islets
Pancreatic polypeptide Orexin	Pancreatic islet cells Smooth muscle, mucosa; Both enteric plexuses and hypothalamus
Somatostatin Somatostatin	D cells in stomach, intestines and pancreas X/A -like endocrine cells in stomach
Ghrelin	
Tachykinin Neurokinins	Enteric neurons

tides, especially NK-1 (substance P and substance K), are often shown to be stimulating motor neurons. In contrast, vasoactive intestinal peptide is invariably an inhibitory motor neuron, often colocalized with nitric oxide. Somatostatin also inhibits many gastrointestinal functions, including absorption, secretion, and blood flow. Neuropeptide Y is found throughout the digestive tract colocalized with sympathetic transmitters such as norepinephrine. Gastrin-releasing peptide not only stimulates the release of gastrin, but within the enteric

nervous system it can function as a transmitter in interneurons. Calcitonin gene-related peptide is most commonly seen as a transmitter in afferent neurons, especially those seen to reach the esophageal or intestinal lumen.

The role of the enteric nervous system, with its highly diverse neurons and complex array of interacting neurotransmitters, emphasizes how incredibly fine-tuned and integrated are the local reflexes of gut motility, secretion, absorption, and circulation.

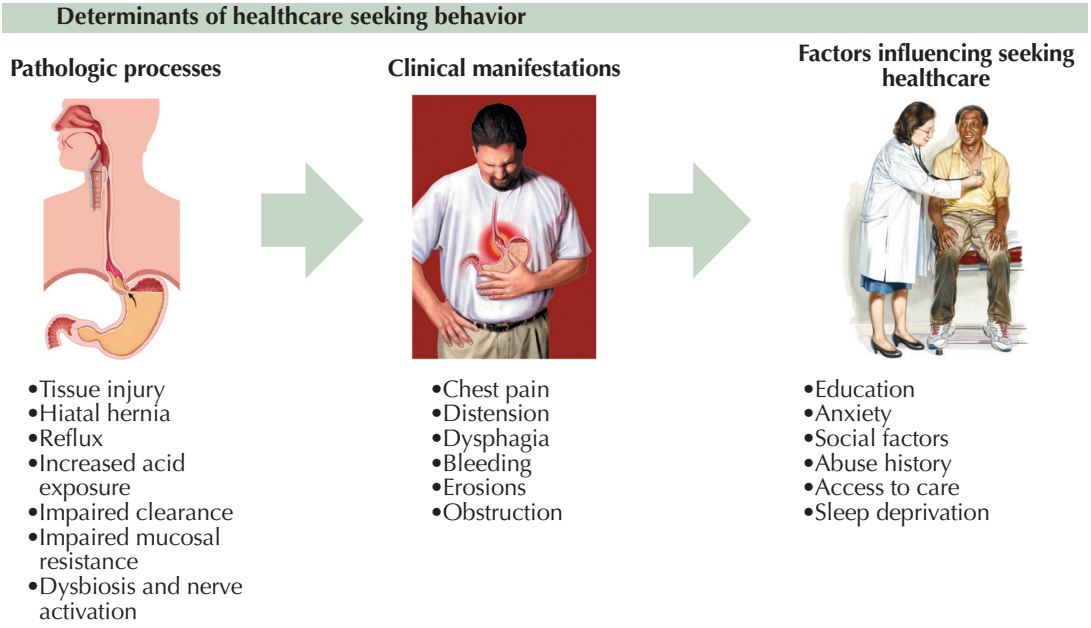
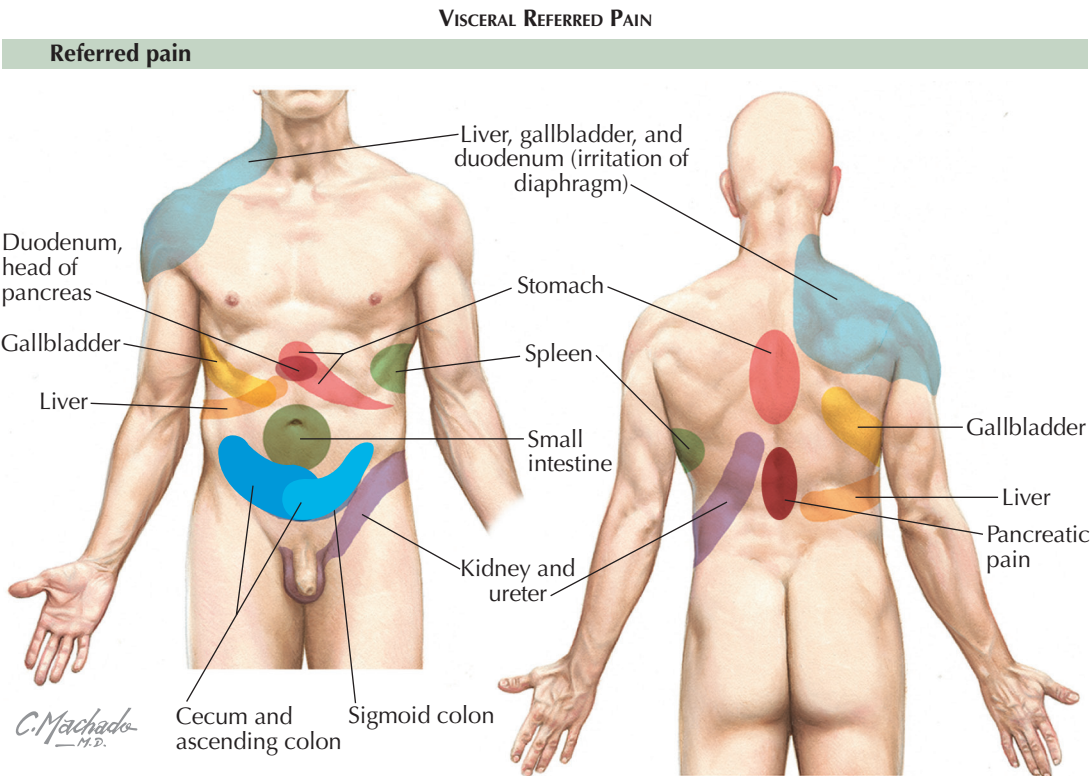
INTERPRETATION OF VISCERAL PAIN

Pain is one of the most important clues to the presence of a disorder in the digestive system. After upper respiratory infections, abdominal pain is the second most common cause of absenteeism from work or school. Of the four cardinal presentations of illness of the digestive system (pain, bleeding, obstruction, and perforation), pain may be the most challenging to interpret. Understanding the physiology and pathophysiology of visceral nociception is essential to developing a well-conceived approach to understanding and diagnosing pain in all of the visceral organs of the abdomen and chest. The first step in interpreting the patient's experience of pain is to characterize its severity, associations, consistency, duration, and location. Pain associated with swallowing, eating specific foods, or defecation but not with exercise is most likely emanating from the digestive system.

Pain is often the most important issue for the patient. Assessing its severity is highly subjective; the clinician must distinguish pain associated with functional disorders from that associated with life-threatening disorders. The severity of pain may be similar in both circumstances. Pain should be described on a scale of 1 to 10, with 1 being minor discomfort and 10 being the most severe pain the patient has ever experienced. Unfortunately, the intensity of pain does not correlate well with the severity of an underlying disorder. For example, patients with esophageal reflux but normal endoscopic findings often experience more severe pain than patients with erosive esophagitis, strictures, or even Barrett esophagus, a premalignant condition of the esophagus. Furthermore, functional pain is often characterized by the patient as unbearable because of the patient's hypervigilance to the digestive system. Some patients ignore early signs of abdominal discomfort only to later discover that they were due to impending obstruction from a severe inflammatory or malignant disorder. Encouraging patients to achieve the right balance between paying attention to the body's messages and ignoring or denying painful signals from the gut can be a key to helping them achieve good health.

Functional pain has been defined as the presence of disordered gastrointestinal function despite a normal gross appearance and anatomy and normal initial blood test results. Functional pain is not indicative of a weak character or weak countenance, nor is it imaginary pain, falsified pain, or malingering. Clarifying that these symptoms are "real" is more difficult for functional pain due to muscle spasms or to subclinical injury such as esophageal spasm, nonerosive esophageal reflux, non-ulcer dyspepsia, biliary dyskinesia, or irritable bowel syndrome, which are characterized by motility disorders that are rarely identified on motility testing, much less on endoscopic or radiologic findings. Diagnosing these and other functional disorders may be attempted as "diagnoses of exclusion." Such attempts are unacceptable for any physician who hopes to keep unnecessary health care expenditures at a minimum.

The severity of pain is influenced by a variety of nonorganic issues, including the patient's psychological state, previous experiences, educational level, and socio-



logic factors. At the same time, it is important to appreciate that dismissing patient symptoms as "functional" all too often leads to missing rare diagnoses such as malabsorption, preventable food reactions or allergies, porphyria, vasculitis, or Crohn disease. For example, for many years, pain was often attributed to the common functional bowel problem of irritable bowel syndrome; now, however, we can easily diagnose the cause of such pain as small intestinal bacterial overgrowth, lactose or other disaccharide malabsorption problems, celiac disease, or nonceliac gluten sensitivity.

Localization of pain is also important. Unfortunately, localization can be very challenging for the patient because of the physiology of visceral nociception. When taking the medical history, the clinician should try to identify the location of the pain at its onset and

determine if it has changed. Pain that is variable and inconsistent in its location, severity, or associations suggests a functional pathophysiology. Pain that is severe in the daytime and at times of stress but absent at night is also more likely functional. In some conditions, the perceived movement of pain may help to localize the source, particularly if the pain is intensifying. The classic example of this is *acute appendicitis*. This acute abdominal emergency often begins with vague pain across the abdomen or in the periumbilical region. When the peritoneum becomes inflamed, the location becomes clearer and usually ends in a point of tenderness in the right lower quadrant over the affected organ known as the *McBurney point* (one third of the distance from the anterior superior iliac spine to the umbilicus).

INTERPRETATION OF VISCERAL PAIN (Continued)

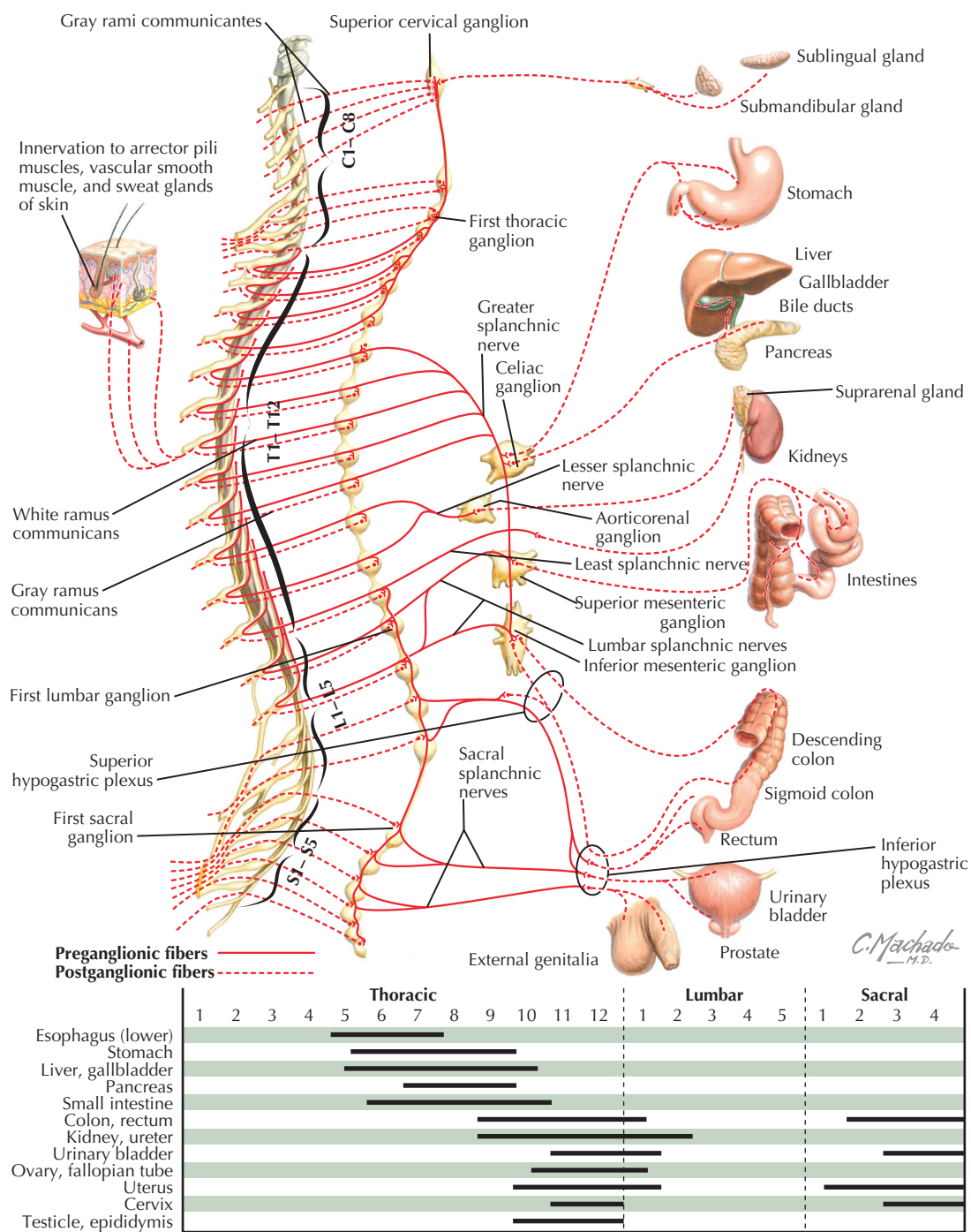
The most likely source of abdominal pain is often suggested by a careful history and physical examination. Four regions should be considered. Determining which side the pain is on is also helpful, but even cholecystitis and appendicitis may present with left-sided pain. Limitation in the ability of the history and physical examination to localize the source of visceral pain is in stark contrast to somatic pain, which can usually be pinpointed to within a few millimeters. These limitations are due to the anatomic and physiologic distinctions between the visceral and somatic nervous systems.

Visceral receptors cannot distinguish the cause of the pain as inflammation, ischemia, malignant or infectious invasion, or distention (the commonest cause). At the level of a receptor, somatic sensation can rely on a host of distinct receptor types of high density in the skin and in striated muscles innervated by the CNS. In contrast, afferent receptors in viscera are sparse and most are naked nerve endings that respond to a variety of stimuli (polymodal). Receptors that are often useful in localizing pain are in muscle spindles in the muscularis propria or encapsulated pacinian corpuscles in the mesentery.

Another factor commonly leading to confusion regarding gastrointestinal symptoms is the tendency of a patient to adapt to chronic and persistent stimuli. Instead of increasing feedback to the CNS, persistent stimulation of gut receptors gradually leads to a distinguished signal output over time. The frequency with which these and other receptors discharge electrical currents gradually decreases over time when a stimulus is persistent. Adaptation may be dangerous when the body no longer recognizes a signal of severe distention from obstipation or invasion from a malignancy.

Nerves carrying afferent information do so through unmyelinated C-type fibers. The nerves may be in the vagus nerves, in which 80% of the fibers are afferent and which terminate in the nodose ganglion. Others travel in the sympathetic system through the dorsal root ganglia from splanchnic nerves (20% afferent) or pelvic nerves (50% afferent). Afferent signals travel to the spinal column in nerves that coalesce with somatic nerves in the dorsal horn. This sets up a relationship between visceral and somatic structures that may create unusual radiation patterns to the musculoskeletal system known as *referred pain*. Examples of viscerosomatic convergence leading to referred pain are gallbladder and liver pain to the right shoulder, esophageal and cardiac pain to the left arm, and kidney pain to the perineum or scrotum. Within the dorsal roots, nerve signals may be transmitted to the CNS bilaterally, a fact that explains why visceral pain is often poorly localized to one side of the body or the other.

Perhaps the most significant limitation of visceral pain is the fact that afferents from each organ enter the spinal column through splanchnic nerves at multiple levels, with multiple other organs. The phrenic nerve therefore carries afferent information from the liver capsule, spleen, and diaphragm through C3-C5; the greater splanchnic from many upper gastrointestinal organs, including the gallbladder, stomach, pancreas, and small intestine, through T6-T9; and the lesser



(From Klein KB, Mellinkoff SM. Approach to the patient with abdominal pain. In: Yamada T, ed. Textbook of Gastroenterology. Philadelphia: Lippincott Williams & Wilkins, 1991, 660-681.)

splanchnic from the colon and appendix, as well as the kidney, ureters, urinary bladder, ovaries, and uterus, through T11-T12. Overlap occurs again at the level of the splanchnic nerves, which innervate multiple organs, including the cervix, testicles, epididymis, sigmoid, and rectum, through T11-L1. This convergence of afferent fields makes it difficult for the patient, much less the clinician, to identify the source of the pain. The *convergent fields* obviate the possibility of a viscerotopic distribution of visceral afferents in the brain, as occurs so precisely for somatic nerves. Only the pharynx and esophagus show any clear viscerotopic pattern. This pattern of distribution occurs within the brainstem near the swallowing centers.

Pain perception may be altered at the level of the spinal cord by inhibitory input from the CNS or spinal

cord. Afferent nerve input to the spinothalamic sensory pathways may be disrupted by inhibitory signals descending from the frontal cortex. This phenomenon can be helpful in a situation in which a patient needs to ignore pain to be able to continue to function. This reflex is similar to the *gate theory* for exceptional somatic nerve and muscle function in times of pain or exceptional need. Such pathways can become maladaptive, however, when a patient uses them to suppress important information that should result in seeking medical care for pathologic symptoms.

In summary, visceral pain is a subjective symptom of great clinical significance that can only be interpreted using a biopsychosocial model rather than a strict medical model and must take into account the many limitations of visceral nociception.

GASTROINTESTINAL HORMONES

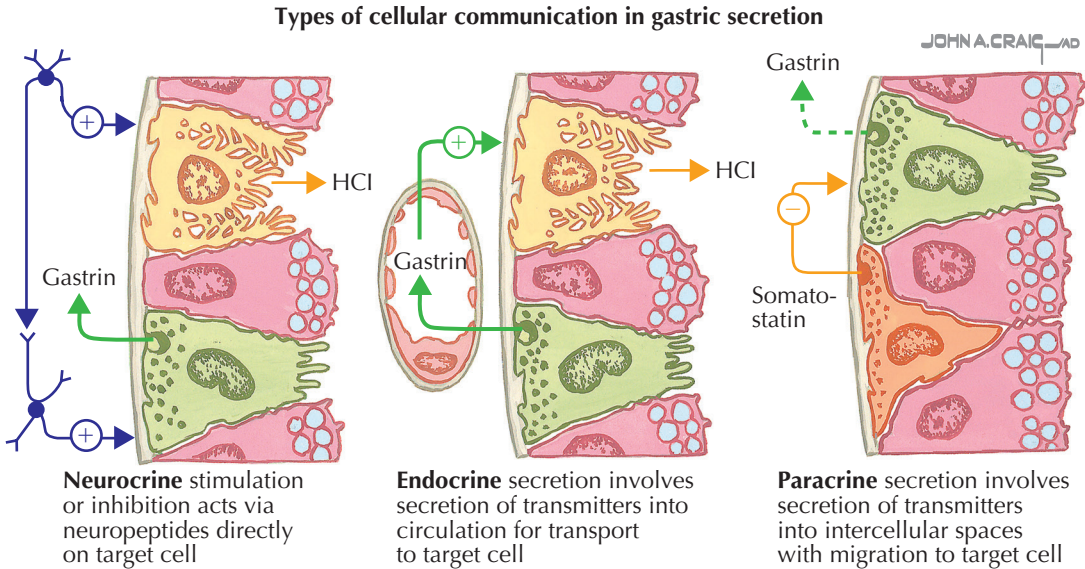
The scientific field of endocrinology began with the discovery of secretin in 1904 by Starling. Since then it has been shown that an incredibly diverse list of digestive tract functions are influenced by a variety of gastrointestinal hormones. Specific functions of gastrointestinal hormones and their respective disorders will be discussed in greater detail in chapters on specific organs. A brief outline of major gut hormones follows, as well as a tabulation of major digestive tract hormones.

The hormones of the gastrointestinal tract are released by three mechanisms. Endocrine cells of the pancreas congregate in Langerhans islets that are intermingled with groups of exocrine cells in the acini and in the ducts. There they release a variety of hormones into the adjacent capillaries. In contrast, most endocrine cells in the digestive system are unlike those in other hormone-secreting organs of the endocrine system which are localized to specific organelles in an organ or make up an entire gland. Enterochromaffin cells containing peptide hormones and nonpeptide transmitters are interspersed between other epithelial cells along the surface of the mucosa throughout the stomach and intestines. The apical border of these specialized cells reaches into the lumen, where microvilli can react to changes in the chemical concentration of intraluminal contents. Gastrointestinal hormones are released from these epithelial cells by three different modalities: (1) They may be released into the local capillaries and thus into the systemic vascular system in a typical endocrine fashion, as occurs in the pancreas; hormones released in this *endocrine fashion* influence other digestive tract functions, the blood flow, or the appetite in response to specific stimuli to the mucosa. (2) Other endocrine cells release their hormones locally, through specific organelles that release directly onto nearby cells in a *paracrine fashion*. (3) Hormones may be released into the interstitial space in a less specific *exocrine manner*. Through these highly specialized mechanisms, hormones are released systemically, locally, or specifically onto nearby targeted cells.

Isolation, sequencing, and molecular analysis of intracellular messaging systems that modify the release of gastrointestinal hormones have revealed just how complex the regulation of these mediators are as they influence gut function. A common feature of gastrointestinal hormones is the complex way in which they are synthesized and processed posttranslationally. The hormones are typically derived from a large pretranslational messenger RNA that may contain more than one hormone sequence. The translational products of these mRNA messages are long peptide chains of prohormones or prehormones. Posttranslationally they are cleaved into hormones of varying lengths, each of which has a different affinity for its receptor ligand (e.g., gastrin may circulate as big-gastrin 36, gastrin 34, or a smaller version of gastrin-8).

Neuroendocrine cells can grow into tumors that may result in complex, often characteristic clinical syndromes. These symptomatic neuroendocrine tumors may occur sporadically or as part of the inherited syn-

Clinically important peptide hormones and associated disease states		
Peptide	Disease state	Clinical correlations
Gastrin	Zollinger-Ellison syndrome – severe peptic ulcer disease, diarrhea	Pentagastrin (analogue) used to assess acid secretory capacity and provoke bioactive neuropeptide secretion in VIPoma and medullary carcinoma of the thyroid
Cholecystokinin	Abnormalities seen in bulimia, celiac disease, delayed gastric emptying	Dynamic gallbladder emptying HIDA scan study to evaluate gallbladder contractility in chronic cholecystitis and sphincter of Oddi manometry for biliary dyskinesia
VIP	Verner-Morrison syndrome (VIPoma) – voluminous diarrhea, hypokalemia, flushing absent in Hirschsprung disease, achalasia	VIP-based radionuclide imaging used to locate and guide resection of VIP-secreting tumors, pancreatic adenocarcinomas, and carcinoid tumors that express VIP receptors
Secretin	Found in neuroendocrine tumors (NETs), but despite being a potent stimulant of pancreatic secretion, isolated syndrome has not been described	Used to assess exocrine pancreatic function; secretin stimulation test used to diagnose gastrinomas; aids in cannulation of pancreatic duct during ERCP
Somatostatin	Somatostatinoma – diabetes, diarrhea, gallstone disease, migratory necrolytic erythema	Octreotide (analog of SN): • Diagnostics – Diagnosis and localization of neuroendocrine tumors • Therapeutics - Secretory diarrheas, variceal bleeding, certain neuroendocrine tumors
Motilin	Not described	Macrolide antibiotics (erythromycin) stimulate motilin receptors and are used in diabetic gastroparesis; also used to clear gastric contents and increase visibility in emergency endoscopy for upper gastrointestinal bleed



drome multiple endocrine neoplasia, which is due to a mutation of the *MEN-1* gene which encodes a cyclin-dependent kinase inhibitor. This autosomal dominant syndrome is associated with tumors of the islet cells of the pancreas, parathyroid glands, and pituitary gland. It may also be associated with tumors of the adrenal cortex, carcinoid tumors, and nonendocrine tumors, including angiofibromas, leiomyomas, collagenomas, lipomas, and meningiomas.

Increased understanding of gastrointestinal hormones has led to a variety of diagnostic and therapeutic uses for them. One of the most valuable tools for localizing and evaluating neuroendocrine tumors is a ¹¹¹indium-labeled radioactive modification of the somatostatin molecule in the “octreotide scan” (somatostatin receptor scintigraphy). Modified somatostatin is also used to treat upper gastrointestinal bleeding from esophageal varices.

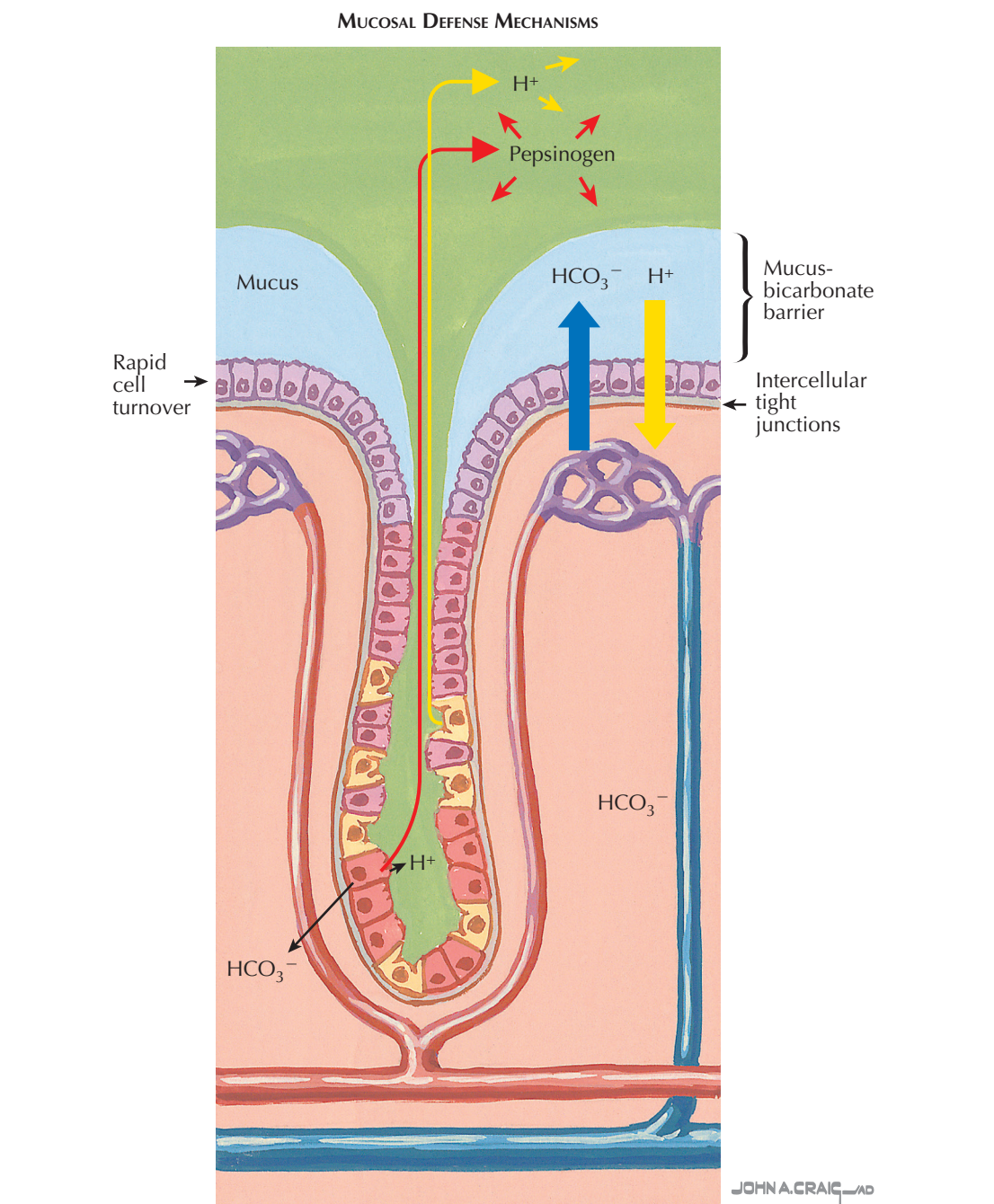
OVERVIEW OF PROTECTIVE MECHANISMS

Many normal physiologic functions necessary for breakdown and processing of ingested nutrients also pose a potential risk to health. These include the normal mechanical forces associated with gastrointestinal motility, extreme acidic content of the stomach, the potent enzymes secreted by the pancreas and intestinal epithelium, the caustic nature of bile salts, and the trillions of intraluminal microorganisms. The digestive system must also have protection from ingested substances that pose a risk to mucosal integrity and health. Even without gross disruption of the integrity of the luminal organs, as occurs with penetrating wound injury or disorders that lead to mucosal ulceration or perforation, there is a constant potential for mucosal invasion at a cellular level.

The digestive system has incredibly complex and intricate immune mechanisms that defend against microorganisms. These immune systems are extensive and include both systems used by the rest of the body and systems specific to the digestive tract, including intraepithelial lymphocytes; specialized M cells; immunoglobulin A (IgA), the gut-associated immunoglobulin submucosal immune cells; and cells outside the digestive system, known as gut-associated lymphoid tissue (GALT) cells.

Epithelial lining cells of the digestive system have highly specific structures designed to prevent back diffusion of intraluminal contents across the epithelium. These include the ubiquitous secretion of mucus, specialized apical surface characteristics, and cell-cell adhesion complexes such as tight junctions. The intraluminal microorganisms pose a great threat, but they also have a protective benefit (see Plate 1-54). There are also a host of nonimmune defense mechanisms at play moment by moment to sustain the integrity of the digestive system in the hostile environment of a “tube within a tube.” We will summarize these other nonimmune defense mechanisms in this section, including motility, secretion, and blood flow.

Motility plays an important role in protecting the digestive tract from damage and in maintaining health. Propulsive contractions of the muscularis propria occur in all luminal organs, including peristalsis, migrating myoelectric complexes (phase III of the interdigestive motor complex), and mass actions in the colon. Most contractions are not propulsive but serve to mix the intraluminal contents and increase their exposure to the luminal surface to facilitate digestion and absorption. In the composite picture, however, the net sum of many propulsive contractions and fewer retrograde contractions results in a net force propelling luminal contents in an oral to anal direction. This prevents regurgitation and limits the accumulation of microorganisms in the upper gastrointestinal tract. Tonic contractions of the sphincters also help to maintain the correct flow of luminal contents. The active mixing and propulsive contractions of the muscularis mucosa and muscularis propria enhance digestion by increasing the opportunity for luminal contents to be exposed to absorptive



Gastric mucosa and submucosa protected from chemical injury by mucus-bicarbonate surface barrier that neutralizes gastric H^+ and by epithelial “tight junctions” that prevent H^+ access to subepithelial tissue. Prostaglandins are important regulators of all these defense factors.

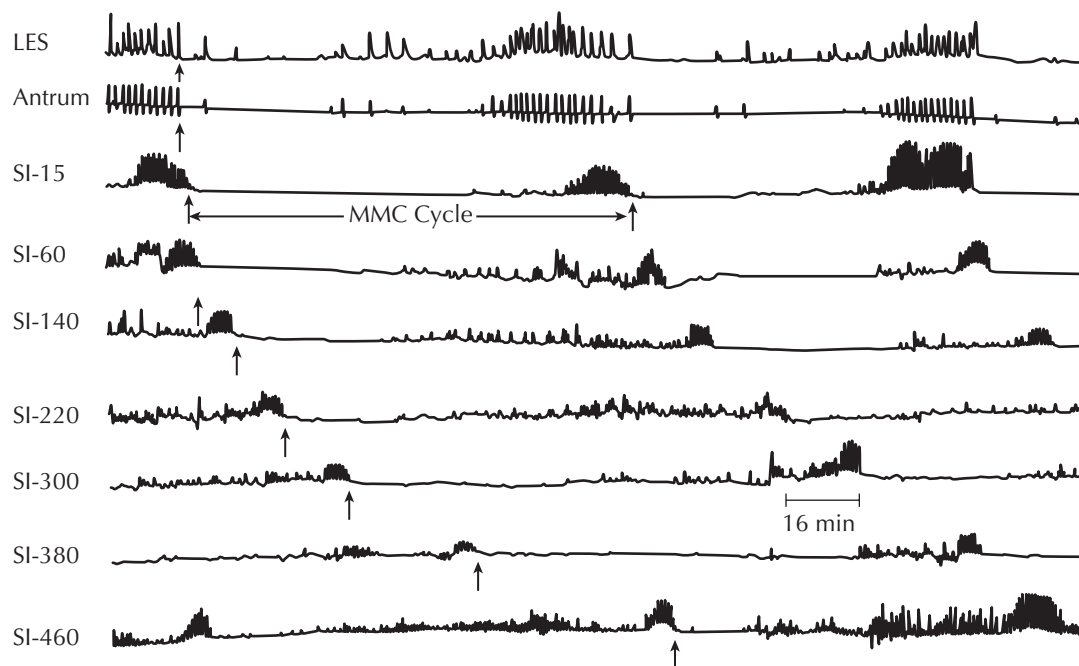
functions and brush-border enzymes and enhancing the diffusion of nutrients in and enzymes out to the lumen by reducing stasis, which could result in increased microorganism concentrations and depth of the “unstirred water layer” (thus, potentially injurious substances are exposed to chemical degradation before they can induce injury). They also protect the mucosa by limiting the duration of exposure of mucosal cells to potentially injurious agents, including organisms, medications, and particulate material, that can have mechanically injurious properties.

Oral, pharyngeal, and upper esophageal sphincter relaxation works in an intricately orchestrated way to propel liquids and solids away from the nasal passages and larynx to protect against nasopharyngeal regurgita-

tion and pulmonary aspiration. The esophageal contractive force moves down the esophagus in less than 10 seconds in a coordinated, single-ring-like peristaltic sequence to propel the swallowed bolus into the stomach. Peristalsis creates a stripping wave to propel the potentially dangerous contents further away from the airway and below the check-valve function of the lower esophageal sphincter. When the sphincter competence is interrupted, a secondary (nonvoluntary) peristaltic contraction pushes regurgitated gastric contents away from the airway and pharynx back into the stomach.

In the stomach, ingested materials are triturated or ground into smaller particulate matter that can be acted upon more effectively by digestive secretions. The

INTESTINAL HOUSEKEEPER



Phase III of the migrating motor complex. When absent or infrequent, small intestinal bacterial overgrowth can develop.

OVERVIEW OF PROTECTIVE MECHANISMS (Continued)

pyloric sphincter serves a “sieving function” that permits only small particles to pass. This creates a soft chyme coated with mucus which can easily pass through to the rest of the digestive tract. In so doing it not only optimizes the surface area for digestion but further reduces the size of particulates to prevent larger matter from interfering with digestion or becoming lodged in the lumen or ileocecal sphincter.

Arguably one of the most complex and fascinating physiologic activities in the digestive system is the pattern of *interdigestive motor complexes* that occurs after digestion of a meal. Initially, after the intense contractile activity associated with mixing and propelling nutrients down the digestive system there is a period of rest. Then, after a brief period of active, mixing (segmental) contractility, the intestinal housekeeper passes from the gastroesophageal junction to the distal ileum or ileocecal sphincter. This sweeping wave of intense contractility provides a mechanism for clearing the stomach and small intestine of any indigestible solids, microorganisms, and waste products to prepare it for the next meal. In so doing, larger particles such as sinew, indigestible food stems, large seeds, or such modern solids as swallowed gum are retained in the stomach during digestion so that they do not interfere with the body’s need to capitalize on all swallowed nutrients, until the housekeeper wave propels them as waste into the colon. This cycle continues in mammals such as dogs every 90 minutes in a strikingly regular way, but it is less regular

in humans. The cycle is interrupted by eating and is initiated through the action of the hormone motilin.

Secretions can both damage and protect the epithelium of the luminal organs. Peristalsis and mixing contractions of the luminal organs can, however, produce incredible forces against the mucosa. To reduce the impact of these forces, epithelial cells and submucosal glands from the mouth to the anus create a thin layer of slimy substances, including mucins, phospholipids, and the trefoil-factor family of peptides, which lubricate the wall and reduce friction. Mucus is synthesized in the Golgi apparatus of surface mucus cells and submucosal cells and packaged into secretory granules that discharge their contents from the apical surfaces of cells. Mucus-secreting cells can also deliver their protective substance into the lumen by accumulating large quantities of mucus in their cytoplasm and then exfoliating the entire cell into the lumen.

Mucus not only provides a protective effect by lubrication but establishes a diffusion barrier that creates a pH gradient above surface mucus cells that face the lumen of the stomach or duodenum; it can contain extraordinary concentrations of acid, to a pH of 1.0 to 1.5. Although the diffusion barrier of mucus alone is ineffective against the diffusion of protons (hydrogen ions from hydrochloric acid), it can effectively slow the diffusion of the much larger molecules of bicarbonate secreted from the surface mucus cells and glands of the stomach. This creates a pH gradient by slowing the diffusion of the much larger bicarbonate ions away from the mucosa, where a much safer pH of 7.0 is seen at the

cell surface; the gastric lumen pH of 1.0 to 1.5 is prevented from injuring the cell.

Secretion of fluids also provides a protective function. The secretion of electrolytes and accompanying diffusion of water by salivary, gastric, duodenal, pancreatic, and gallbladder epithelia dilute ingested nutrients to facilitate digestion and transit. It also provides a means of diluting potentially injurious chemicals and disperses them for processing by other defense mechanisms. Secretion of high concentrations of hydrochloric acid by gastric parietal cells creates a pH of 1.0 to 1.5. This solution protects the body from potentially injurious organisms by effectively killing microorganisms that are ingested or that grow in the oral or aerodigestive cavities. This environment sterilizes intraluminal contents in the stomach and duodenum. When acid secretion is decreased by medications or gastric atrophy, there is an increased risk for infection and for small intestinal bacterial overgrowth. The latter can lead to bile salt deconjugation and competition for nutrients, most notably vitamins such as B₁₂. Digestive enzyme and bile salt secretion also reduces the survival of all but the most resistant microorganisms.

Each of these nonimmune defense mechanisms depends on rich mucosal blood flow to occur. When this blood flow is reduced by the ‘mucosal steal’ that occurs as a result of hypotension or sympathetic overload, the risk for mucosal injury is increased. Regulatory messengers that enhance mucosal protective mechanisms, including blood flow, such as prostaglandins, are also critical for maintaining mucosal health.

IMMUNE DEFENSES OF THE DIGESTIVE SYSTEM

It has often been emphasized that the digestive system “tube” is the host to a very hostile intraluminal environment that is actually not part of the organism itself. This tube includes microorganisms and chemicals that if not kept in check can quickly result in the patient’s death. It is critical for health that the luminal organs have mechanisms that are highly selective in identifying foreign antigens and thus prevent the invasion of luminal microorganisms through or between epithelial cells into the submucosa, where they can invade the rest of the body. This system must also be able to distinguish between harmless commensal organisms and organisms that cause disease. The extensive, specialized system of immune cells that constantly defend against luminal attack with a perpetual state of controlled inflammation described in this section is known as the GALT system. If the GALT system is not effective, microorganisms can invade; if it is overly active, autoimmune disorders result, such as chronic gastritis, celiac disease, or inflammatory bowel disease. Other defense mechanisms are discussed with [Plates 1-50, 1-51, 1-53, and 1-54](#).

Epithelial cells provide the first line of both mechanical and immune defenses. This is possible because the cells not only have specialized qualities that prevent fluid and bacterial movement through or between cells, but they can also process antigenic material and function as antigen-presenting cells.

Lymphocytes are the next line of defense in the digestive system. In fact, there are over a trillion immune-active cells in the gut, making it by far the largest lymphoid organ in the body. A fascinating, distinct subclass of lymphocytes, the intraepithelial lymphocytes, migrate into the intercellular space between epithelial cells. There they provide an important cytotoxic and antiviral line of defense but play little, if any,

role in processing the immune response cascade. This is achieved by a wide variety of lymphocytes, macrophages, and dendritic cells found in the lamina propria of the intestinal organs, and to a lesser extent in the stomach. The esophagus has lymphocytes, but in a normal state has no eosinophils, mast cells, or polymorphonuclear cells.

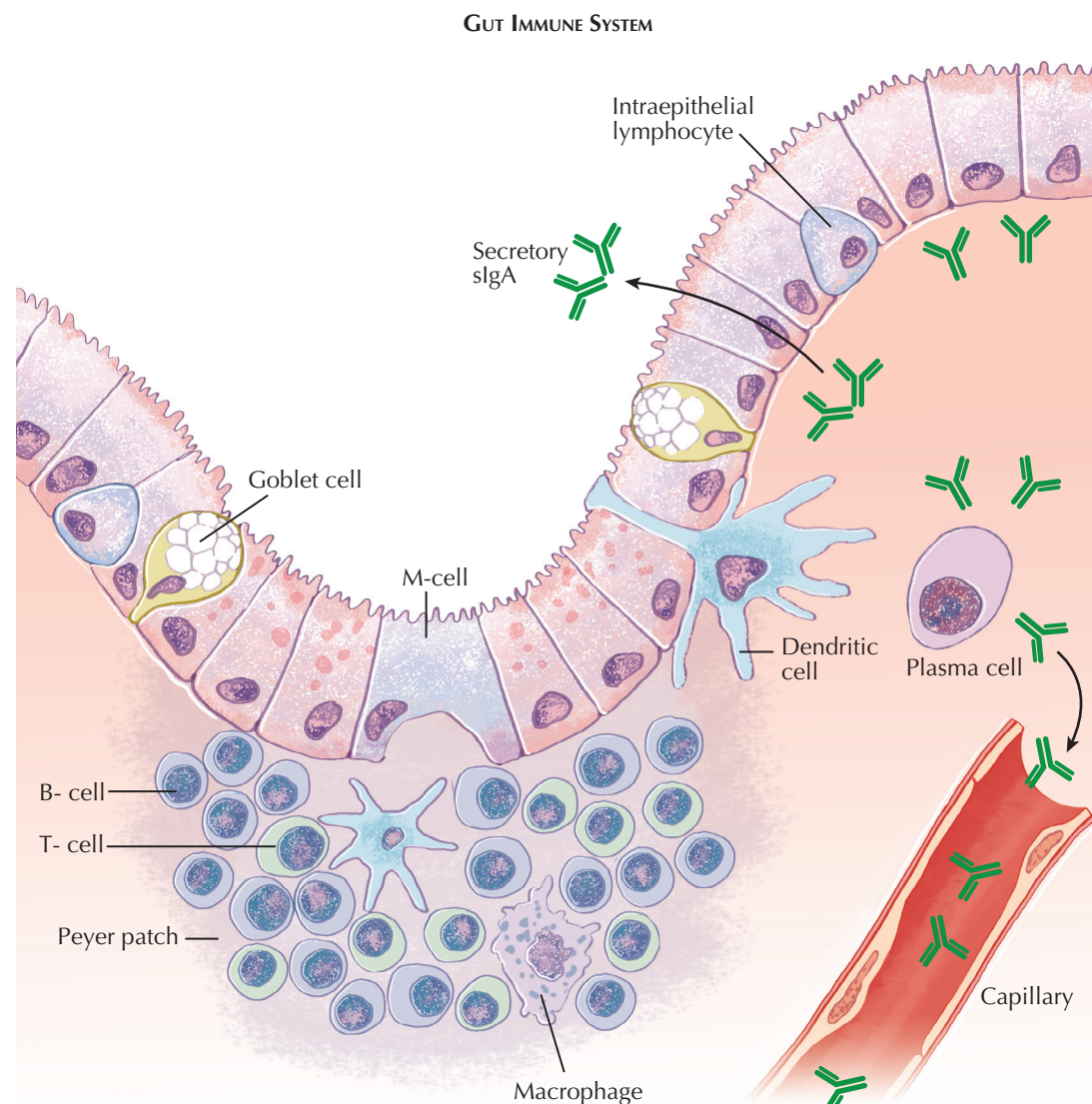
Terminally differentiated B lymphocytes become plasma cells in the lamina propria, where they are the major source of IgA. IgA synthesized in the gut can be released in monomers into the circulation. IgA is also secreted into the lumen of various organs, including the gut, as secretory IgA in the form of dimers, which are two IgA molecules coated with a specialized secretory component that prevents enzymatic digestion. Secreted IgA dimers are kept near the surface by becoming trapped in the mucus glycocalyx. Intraluminal secretory IgA that reaches the distal ileum can be reabsorbed and transported to the Kupffer cells of the liver, where the antigen can be destroyed and the secretory IgA released into the bile, and thus circulated back to the intestinal lumen.

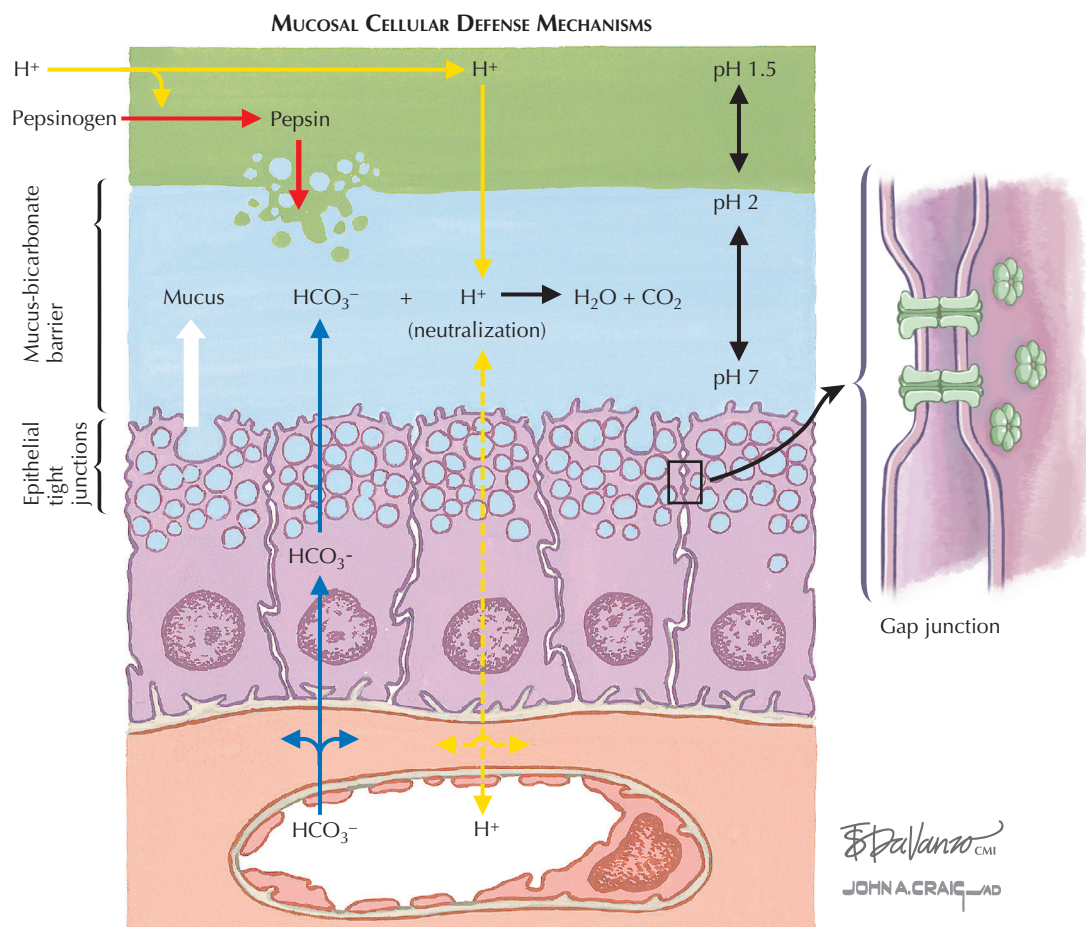
Dispersed between epithelial cells of the small intestine can be found highly integrated antigen-processing structures consisting of modified microfold epithelial

cells (M cells) and their adjacent lymphoid follicles, or Peyer patches. A Peyer patch is a highly active accumulation of macrophages, dendritic cells, and T and B lymphocytes which can evaluate antigens and even whole microorganisms brought across the epithelium through the porous M cells and their adjacent specialized epithelial cells. Submucosal dendritic cells independent of M cells also play a key role as antigen-presenting cells. Once activated, B-cell and T-cell blasts can leave the Peyer patch and enter the circulation or be carried by the lymphatics to adjacent nodes or to the bloodstream.

Another important part of the immune defense systems for the digestive system are the large numbers of lymph nodes found throughout the mesentery and the larger accumulations of lymph glands at the base of the three major sources of arterial blood to the gut, the celiac, superior mesenteric, and inferior mesenteric arteries.

Finally it must be remembered that the liver is second only to the small intestine as the second largest reticuloendothelial organ in the body. Antigens and microorganisms that escape other gut defenses are carried to the liver, where they can be filtered from the blood by sinusoidal Kupffer cells.





EPITHELIAL CELL DEFENSE MECHANISMS OF THE DIGESTIVE SYSTEM

The potential for intraluminal contents to cause severe, even lethal, injury to the patient warrants highly specialized and effective cellular and noncellular defense mechanisms against the “tube within the tube.” An increasingly recognized characteristic of individuals who are susceptible to digestive diseases is the degree to which the epithelial lining provides an ineffective barrier and, thus, a “leaky gut.” This occurs in patients with Crohn disease, celiac disease, food allergies, and food intolerance.

The first line of defense from intraluminal contents is the partial barrier created by the glycocalyx coat secreted by submucosal glands, goblet cells, and epithelial cells throughout the length of the gut. This thick mucoid substance is a complex mixture of mucins, glycoproteins, and trefoil factor–like peptides. Its slippery nature serves as a lubricant to reduce the shearing forces produced by contractions and swallowed solids. In the stomach, mucus retards the diffusion of bicarbonate away from the epithelium to create a pH gradient that ranges from 1.0 at the surface of the mucus to a neutral 7.0 at the epithelial cell surface. In the intestine, it serves to retard diffusion of foreign antigens and microorganisms toward the surface while retaining secretory IgA molecules that have been released into the lumen, at the surface. This glycocalyx can also trap antigens within this sticky material to eventually be passed in stool.

The heterogeneous cells lining the gut all share the ability to provide an effective physical barrier that is resistant to invasion of microorganisms and toxins and to diffusion of electrolytes. Intestinal epithelial cells can

also influence the immune response by secreting pro-inflammatory mediators, including cytokines, chemokines, and adhesion molecules. They can also process invading microorganisms or absorbed toxins, neutralize them, and then serve as antigen-presenting cells to T cells in the lamina propria’s immune system. Finally, it is important to mention the intricate systems within epithelial cells that are able to recognize when a cell is being overcome by antigen excess, triggering intracellular messengers to produce apoptosis. These dying cells are extruded constantly into the lumen and replaced by new, healthy cells. Interposed between epithelial cells are podocytes of subepithelial dendritic cells, which are highly efficient antigen-presenting cells.

Microorganisms can invade the gut by crossing epithelial cells (transcellular) or by passing between cells in the process of translocation. Key to preventing such invasions are the cell-cell adhesion molecules, particularly tight junctions (zonulae occludentes). Tight junctions are complex yet dynamic structures that selectively control the paracellular movement of antigens and fluid to the underlying intraepithelial lymphocytes and lamina propria. When these gates to the paracellular space’s protective mechanisms are impaired, cells can become damaged. In the upper gastrointestinal tract, medications commonly damage tight junctions, permitting back diffusion of acid and submucosal injury that can lead to ulcerations. In the intestine, translocational invasion is partially controlled by intraepithelial lymphocytes.

The ongoing “controlled inflammatory response” associated with the epithelial cell damage, apoptosis, and exfoliation is occurring constantly to maintain an effective biologic shield against its external environment within the tube of the gut. Cell replacement must be common and robust to provide the billions of healthy epithelial cells that coat the gut. When ongoing cellular replacement is impaired, health is threatened. In the esophagus, the nonkeratinized squamous cell epithelium is under the constant influence of shearing forces related to swallowed food and strong esophageal contractions as well as the caustic effects of gastroesophageal reflux. The increased rate of cellular replacement in response to injury can be identified by the enlargement of the rete pegs. Mucosal breaks, ulcerations, and bleeding result when this cellular replacement process is overwhelmed. Inadequate replacement of the columnar epithelium of the stomach and intestines occurs commonly in a more wholesale fashion in the setting of hypotension and shock. In shock, the normally robust supply of nutrients and oxygen provided to the gut by its rich vascular supply is diverted to the heart, kidneys, and brain. Under such circumstances, if cells continue to be damaged but are not replaced rapidly enough, the gut’s integrity can be lost. When this occurs in the stomach, diffuse hemorrhagic gastritis may result. In the gut, mesenteric ischemia leads to increased leakiness and translocation; if it is not corrected, it results in the many potentially lethal complications of mesenteric ischemia, including sepsis, bleeding, and, if not corrected, perforation.

MICROBIOME

Microbiota have long been known to be an unseen, ubiquitous majority teeming on every imaginable surface upon and within the human body. These surfaces include the (1) conjunctiva, (2) skin, (3) respiratory tract, (4) gastrointestinal tract, and (5) genitourinary passages. The approximately 100 trillion bacteria in the human body form 2% to 3% of the average body mass and 55% of the dry feces mass, far outnumbering the 10 trillion human cells. Their aggregate metabolic activity has earned them the collective name of the “forgotten organ.”

Contrary to popular belief, many bacteria can be cultured, but the cumbersome techniques and long incubation periods needed for culture have previously prohibited the easy identification of bacteria and, in turn, prevented scientific researchers from grasping their clinical significance. The advent of deep 16S RNA sequencing has dramatically enhanced our ability to simultaneously and accurately identify the presence of individual species. Complementing this technology are the budding sciences of metabolomics and proteomics, which aim to interpret the clinical impact of the metabolites and proteins generated by living organisms and tissues. These technologies will reshape our understanding of how microbiota affect human health and disease.

Importantly, this commensal community does not consist of bacteria alone but also contains countless fungal and viral agents that cohabitate within an intricate mucosal mosaic. Maintenance of this complex interplay is thought to be critical to maintaining mucosal integrity and overall health. On the one hand, innate immunologic and physiologic mechanisms maintain a healthy community that prevents pathogenic organisms from flourishing. On the other hand, multiple microbiota mechanisms promote mucosal integrity and host health.

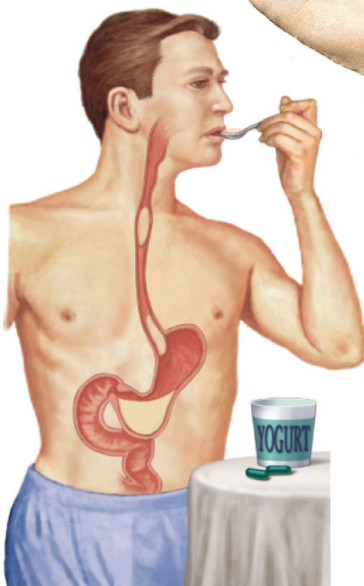
Mucosal surfaces throughout the body demonstrate convoys of leukocytes regularly deployed for surveillance and phagocytosis of microbial offenders. Salivary enzymes contain lysozymes, IgA, and peroxidase, which begin the antimicrobial breakdown. The harsh acidity of gastric secretions is bactericidal. Bile salts serve as detergents and, via micellar formation, envelop organisms, inhibiting their direct mucosal binding. Pancreatic enzymes break down elements of bacterial cell walls. And, of course, the migrating motor complex regularly flushes out intestinal segments, preventing stagnancy and bacterial overgrowth.

Indeed, a constant drama of urban microwarfare is unfolding, in which healthy and pathogenic organisms compete for domination and nutritional resources. For instance, some species will compete for mucosal binding sites to prevent more invasive pathogenic bacteria from invading and causing illness. In fact, bacteria are known to secrete lactate, peroxide, and even their own antimicrobial peptides known as bacteriocins, which serve to keep adjacent competitors at bay.

Numerous clinical correlates exist to impress upon medical science how critical these microorganisms are to good health. Initially, a newborn possesses a sterile gut. It is theorized that early luminal exposures between the patient's innate lymphoid system and consumed nutritional elements, including ingested and inhaled microbiota, will go on to shape the future development of health and/or disease. For instance, newborns born via cesarean section rather than natural vaginal delivery are at increased risk for atopic illnesses such as asthma. Infants who are formula fed rather than breast fed are at increased risk for allergic disorders. Gut bacteria play an important role in vitamin K and biotin synthesis.

The variety and number of microorganisms that reside in the digestive tract is highly diverse. The microbiota changes with many factors including diet and medications and with hormonal changes, particularly in the vagina. Numbers express numbers of microorganisms per mL as CFU/mL (colony forming units).

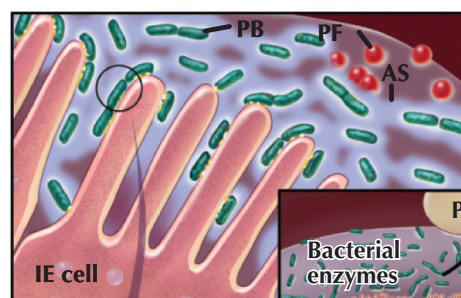
Probiotics



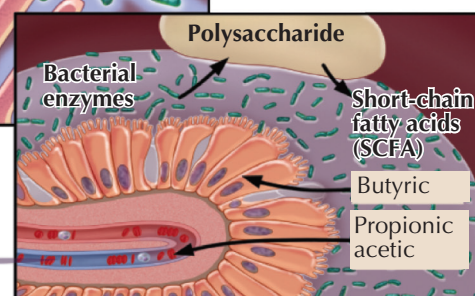
Capsules or yogurts containing live microbial food supplements (lactobacilli or bifidobacteria)

Adherent substances bond probiotic bacteria (PB) to intestinal epithelial cells (IE cell). Antimicrobial substances (AS) antagonize carcinogenic and pathogenic flora (PF)

Ileum



Stimulated immunity and SCFA absorption



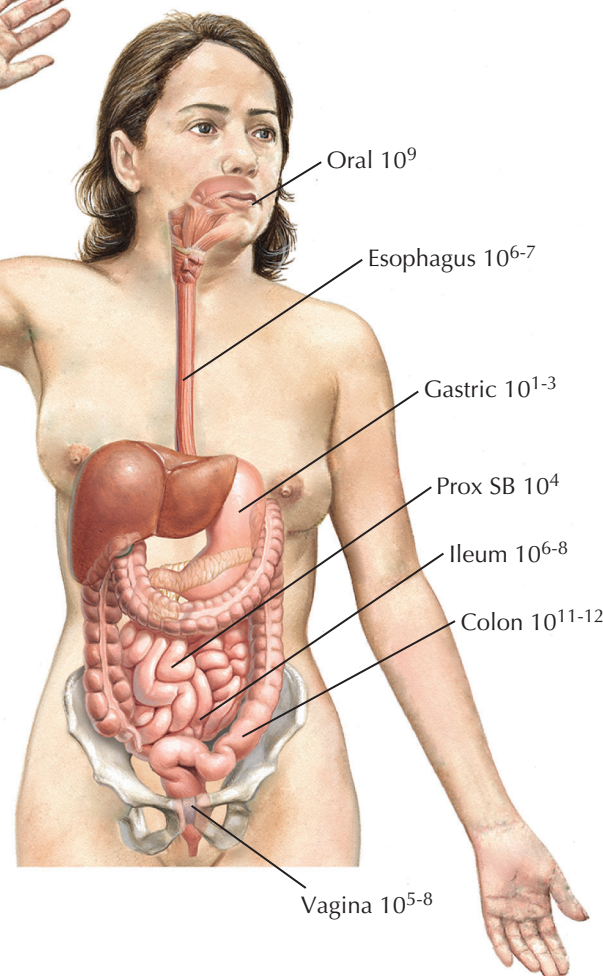
Probiotic bacteria produce enzymes that ferment polysaccharides

They also extract short-chain fatty acids from dietary fiber, specifically butyrate, which promotes colonocyte health. The nonspecific action of antibiotics disturbs the healthy balance of microbes in the colon; this has given rise to epidemics of severe *Clostridium difficile* infection. Reintroducing healthy donor stool suspensions into an actively infected *C. difficile* patient reverses this dysbiosis to a healthy balance with a high rate of clinical cure. Also, periodontal science has demonstrated that individuals with tooth and gingival disease are at double the risk for having coronary artery disease versus their counterparts with a healthy mouth. There

is also a suggestion that intestinal microbiota may influence psychiatric disease; this has given rise to the development of potential psychobiotics.

Countless studies have provided evidence that the microbiota influence the immune system via direct and indirect mechanisms. Other disease states implicated include rheumatologic disease, metabolic syndromes, obesity, and irritable bowel syndrome. The microbiota represent a new frontier for therapeutic exploration that may allow us to moderate chronic illness via traditional medication and therapeutic multistrain collections of microbiota.

MICROORGANISM CONCENTRATIONS (in CFU/mL)



C. Machado
M.D.

K. Carter

ADVERSE EFFECTS OF MEDICATIONS ON THE UPPER DIGESTIVE SYSTEM

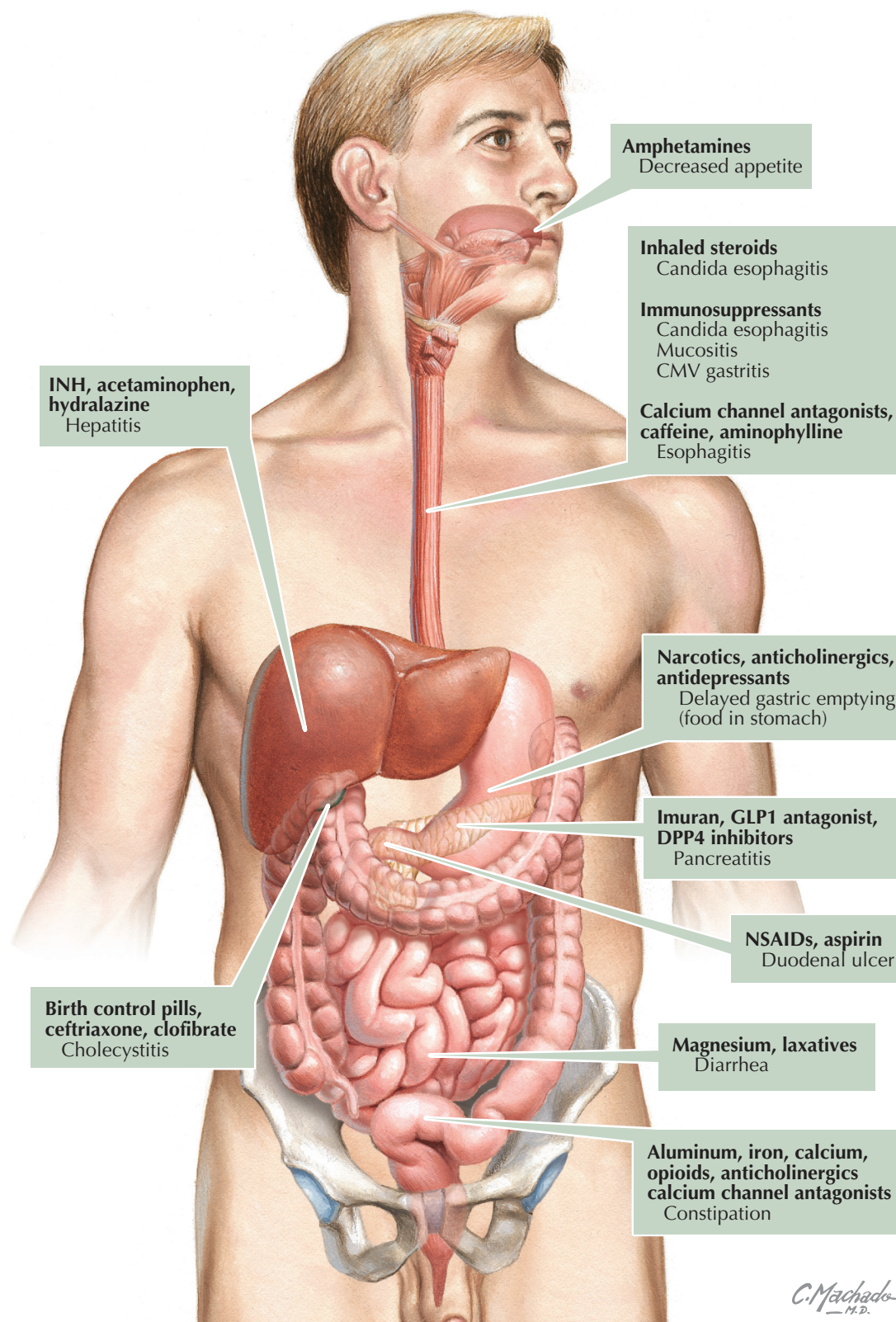
Many drugs adversely affect digestive system function or mucosal integrity. Drug-induced liver injury is so common that we have devoted an entire section of Part III to this topic. Although a host of medications have the unwanted potential for injuring the liver, the wise clinician will consider all medications as potential causes of hepatic injury. Similarly, hydralazine, azathioprine, several agents that effectively treat HIV infections, some antibiotics, and even steroids are known to injure the pancreas. In a patient being evaluated for the cause of acute pancreatitis, recently started medications should be considered; importantly, a medication taken for months may also cause pancreatitis.

The most common mechanism of drug injury to the digestive system is alteration of the integrity of the epithelial lining. Drugs may have a direct injurious effect or may mediate the impaired mucosal defense by indirect mechanisms. Thus, every assessment of a patient presenting with a digestive organ problem must include a detailed history of both prescribed and over-the-counter medications. This history should also include dietary supplements and herbal agents.

The common and all-too-often life-threatening adverse effects of nonsteroidal antiinflammatory drugs (NSAIDs), including aspirin, are so important that we have discussed them in considerable detail with Plate 4-51. NSAIDs are the agents that most commonly cause mucosal injury, but a wide variety of other unrelated drugs also cause direct mucosal injury. These include iron supplements, potassium supplements, bisphosphonates, tetracycline antibiotics, and quinidine. It has been shown that drinking 6 to 8 ounces of fluid before and after swallowing these medications will reduce esophageal injury. The theory that food may act as a buffer against the adverse effects of these drugs in other organs is a reasonable but unproven one. Iron supplements not only can cause mucosal injury but also may raise concern for bleeding when the stool turns dark gray, suggesting melena. In such cases, intravenous supplementation, although more expensive, may also be more prudent.

Drugs that are antimetabolites often interfere with mucosal integrity by reducing the normal defenses provided by the normally high frequency of cell turnover. This is particularly true where cell turnover is most rapid, as in the oral epithelium, distal esophagus, and stomach; aphthous ulcers and even mucosal sloughing can be seen in these areas. Methotrexate and chemotherapeutic agents are most commonly associated with such injury. Irradiation will cause a similar lesion, through the same mechanism. In addition to this acute injury caused by inhibition of cell turnover and repair, irradiation often leads to mucosal atrophy, submucosal bleeding, endarteropathy, vascular ectasias, and mucosal bleeding.

Motility is commonly altered by medications. Medications with anticholinergic side effects can impair the motility function of most, if not all, of the luminal digestive organs, reduce esophageal clearance by reducing peristaltic amplitude, cause increased reflux by reducing lower esophageal sphincter tone, delay gastric emptying, and impair motility of the small and large intestines. Caffeine primarily causes an adverse effect by selective reduction of lower esophageal sphincter tone. Opioids most commonly lead to gastrointestinal symptoms by causing constipation due to the density of opioid receptors in the colon, but can also delay gastric



emptying and cause gastroparesis. The effects of anticholinergic drugs on the motor and secretory activities of the intestine are sometimes the primary therapeutic aim and sometimes an unwelcome by-product of therapy directed elsewhere. Hormones can also impair motility. Most notably, somatostatin analogs delay gallbladder emptying and progesterone has an inhibitory effect on colonic contractions.

The *parasympathomimetic* drugs (e.g., *methacholine*, *bethanechol*), including those agents that inhibit the

hydrolysis of acetylcholine by blocking the action of cholinesterase (e.g., *neostigmine*), *stimulate* saliva production and gastric emptying.

Drugs that either *stimulate* or *inhibit* the effects of *sympathetic nerves* are far less active on the gastrointestinal tract than on other systems. A potent vasoactive sympathomimetic used in a critical care setting, however, often reduces gut blood flow, particularly to the stomach, which can lead to gastritis and delayed gastric emptying.

HUNGER AND APPETITE

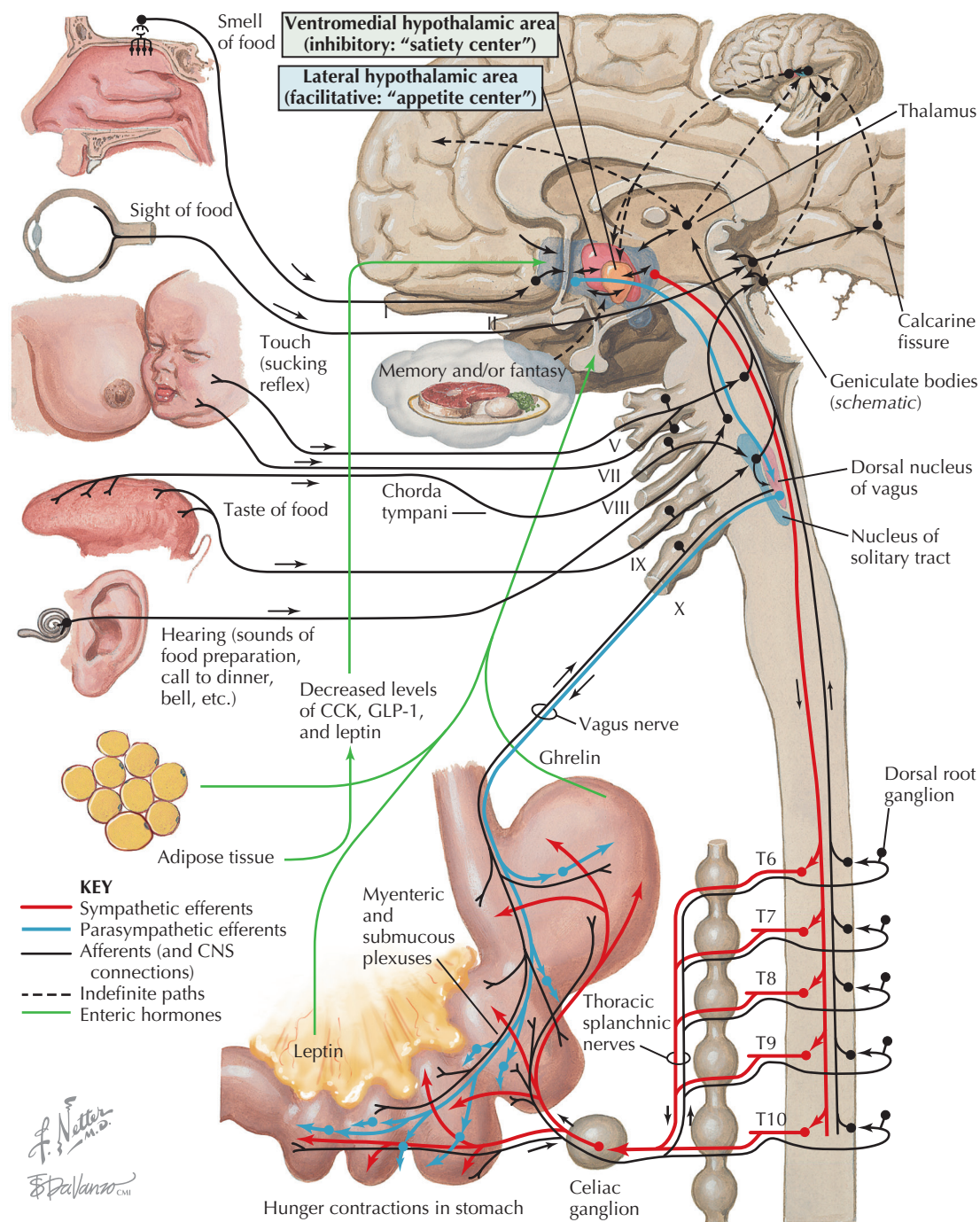
Food intake is due to a complex interplay of emotional factors, learned behaviors, CNS regulation, fat cell thermoregulatory effects, and the digestive system. It has become increasingly clear that the intake of food is influenced by what appears to be an adipose “set point,” which results in a relatively stable weight in most individuals despite efforts to change their weight. The ingestion of food occurs in response to need (hunger) or desire (appetite). *Hunger* describes the complex behavioral responses evoked by depletion of body nutrient stores required for metabolic needs. Studies by Pavlov and his colleagues in the early 1900s emphasized the importance of cortical functions and the vagus nerve through learned behaviors and their associations with food intake. The fact that food-seeking behavior is manifested in the unconditioned state, as in newborn or anencephalic infants or decerebrate animals, emphasizes the important role of lower brain functions, including the reticuloactivating system and hypothalamus.

The digestive system has a major influence on appetite and hunger. A common sensation described by patients as hunger is discomfort localized to the epigastrium and perceived as emptiness, gnawing, or tension. The fact that such ‘hunger pangs’ are experienced by individuals whose stomach has been removed or denervated is evidence that *hunger contractions* are not simply related to gastric contractions. On the other hand, it is clear that the stomach is the major source of the hormone *ghrelin*, which is an important stimulant of food intake. This 28-amino acid peptide is released from X/A-like cells in the oxyntic glands of the gastric fundus but is also found in the pancreas and small intestine. It is structurally related to motilin. Its release leads to increased gastric smooth muscle contractions and stimulation of CNS appetite centers that stimulate food intake.

Anorexia is not a common symptom in patients with complete denervation of the small intestine, as occurs in small bowel transplantation. On the other hand, hormones released as part of the phenomenon known as the *ileal brake* have a significant influence on appetite, including *peptide YY3-36*, which suppresses food intake. Surprisingly, basal levels and postprandial levels of peptide YY are decreased in obese patients.

A variety of other gut neuropeptides influence food intake. Neuropeptide Y, released from the pancreas as well as the hypothalamus, increases food intake. Insulin can also increase food intake. Cholecystokinin, released primarily from the duodenum, reduces food intake.

In addition to influences from the CNS and digestive system, adipose tissue also regulates appetite. The key appetite suppressant *leptin* is synthesized and released from adipose tissues. Leptin is a hormone with extraordinarily broad influences on metabolism, growth,



angiogenesis, and other functions; it appears to primarily serve as the *satiety hormone*. Leptin modifies appetite primarily through its release by white adipose tissue but is also synthesized and released by brown adipose tissue, skeletal muscles, the placenta, ovaries, mammary epithelial cells, and bone marrow. In the digestive tract, it is released by cells in the gastric fundus and by gastric chief cells. It acts as an internal modulator of energy homeostasis, metabolism, and cell replication. Although its primary effects are thought to be mediated by its effects on the hypothalamus, especially on serotonin cells, there are leptin receptors throughout the body on many types of cells. It is clear that leptin release is suppressed by fasting, well before fat stores per se are altered, and is increased by stress, insulin, and corticosteroids and, paradoxically, in obese persons.

Fat stores, particularly of brown adipose tissue, also influence appetite. Brown adipose tissue plays a major role in thermogenesis and appears to be regulated by the CNS hormone *orexin*. It may be more involved with energy expenditure than appetite per se. Orexin is a neuropeptide hormone structurally related to the gut hormone secretin. It is also released from the hypothalamus and is responsible for both arousal and appetite. It increases lipogenesis. In addition to the hypothalamus, it is also present in neurons throughout the CNS. Orexin release is inhibited by leptin and increased by action of the gastric hormone ghrelin. Decreased orexin can lead to a feeling of lowered energy which may cause a person to eat more to acquire energy. Such reflexive food intake in the setting of reduced energy expenditure can contribute to obesity.

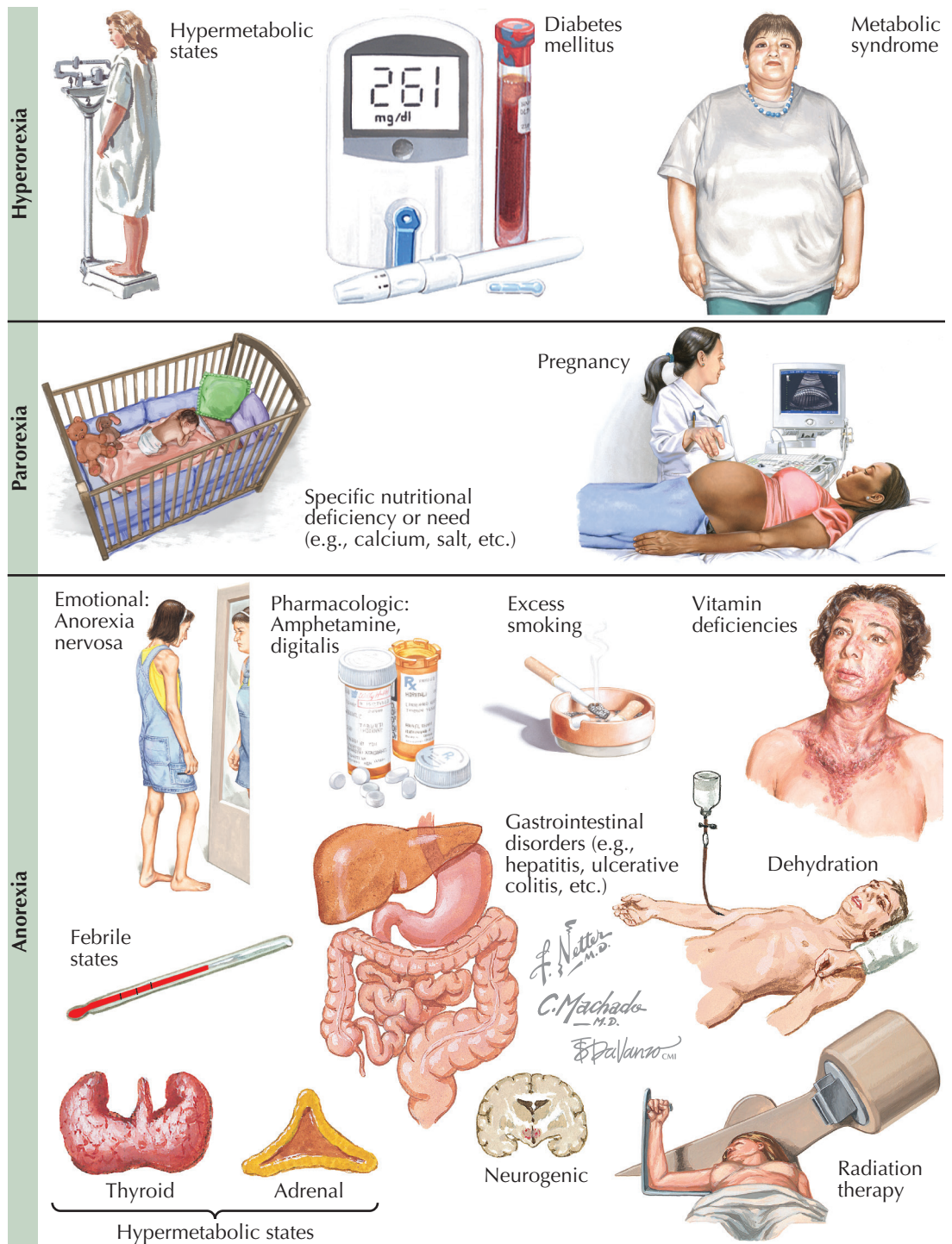
DISTURBANCES OF HUNGER AND APPETITE

In addition to the broad sociologic and economic influences on access to and intake of nutrients, food intake is influenced by (1) volition, learned behaviors, and psychiatric disorders; (2) gastrointestinal and systemic hormones; (3) the microbiome; (4) CNS regulatory mechanisms; (5) the presence of gastrointestinal or systemic diseases; and (6) functional or mechanical digestive tract disorders that retard the normal flow of intraluminal contents. Some individuals have an amazing ability to lose weight by reducing calorie intake, but diets in general have had a disappointingly limited long-term impact on the management of obesity. Brain-gut communications with ghrelin, leptin, cholecystokinin, (CCK), GLP-1, neuropeptide Y, and orexin are potent mediators of appetite (see [Plates 1-46 and 1-56](#)). In the CNS, serotonin and neuropeptide Y pathways are particularly active. Learned behavior and visual, olfactory, and auditory stimuli initiate reflexes via cortical connections to the hypothalamus and limbic system. These complex mediators interact in ways that are incompletely understood to lead to a variety of specific eating disorders.

Polyphagia, overeating, binge eating, and obesity are among the most important issues influencing our society. *Hyperorexia*, or food intake in excess of body requirements even when it poses a severe risk to health, is a formidable medical challenge. It is the most common preventable cause of a host of malignant, endocrine, cardiovascular, musculoskeletal, and respiratory disorders, as well as of cirrhosis and hepatocellular carcinoma associated with a fatty liver. In some persons, such behaviors may be a reaction to stress, obsession, or depression, but it is clear that learned, inherited, and acquired factors influence overeating, as do genetic influences. The fecal microbiota, acquired during childhood and altered by antibiotics, influence the risk for obesity. The hyperorexia of diabetes and hyperthyroidism does not result in obesity, because nutrient stores have been depleted by concomitant nutritional wastage or energy expenditure.

Anorexia describes any state in which the severe depletion of body nutrients fails to lead to adaptive behavior. The appetite is commonly impaired in systemic disorders and disorders of the digestive tract, including neoplasms, pancreatitis, hepatitis, and colitis. The release of tumor necrosis factor alpha, interleukins, and corticotropin-releasing hormone in these disorders contributes to anorexia. Once poor intake has caused calorie deficiency, ketone excess may lead to further anorexia and food deprivation. The hormone orexin has an important contribution to impaired appetite in systemic diseases. Severe nutritional deficiency leading to pancreatic and epithelial atrophy can further exacerbate inadequate intake with malabsorption.

Several psychiatric disorders can lead to impaired, even life-threatening, inadequate food intake, including bulimia and anorexia nervosa. *Anorexia nervosa* is loss of appetite amounting to a disgust or distaste for food and a fear of gaining weight. The patient has intense concerns about the body habitus and a phobia about being overweight or gaining weight. Severe forms of anorexia lead to nutritional and metabolic deficiencies, fluid and electrolyte deficiencies, cachexia, osteoporosis, infertility, amenorrhea, heart damage due to a beriberi type of condition, and death. Gastric emptying is often delayed in such malnourished patients but should not be interpreted as the primary disorder.



Bulimia is a related condition in which the patient restricts nutritional intake by self-induced vomiting after a meal, often in a surreptitious manner, or by purging with laxatives. *Rumination syndrome* and *cyclic vomiting* are related disorders. Management should always include psychiatric consultation by experts in eating disorders. Hospitalization and enteral feeding may be necessary in severe cases. Although the causes are multifactorial and incompletely understood, genetic factors are often involved.

Decreased appetite resulting from food aversion is known as *sitophobia*. This is common in patients with painful swallowing (*odynophagia*) and other conditions that result in pain in response to food intake, such as gastritis and gastric ulcers. *Odynophagia* results from breaks in the oropharyngeal or esophageal mucosa.

Impairment of appetite with excessive smoking may be due in part to impairment of taste sensations. Impaired appetite is also common in patients with *xerostomia* following irradiation or with *Sjögren syndrome*.

Street drugs, particularly cocaine, methamphetamines, and other stimulants, are potent appetite suppressants and should be considered in the differential diagnosis of all patients with anorexia. Similarly, marijuana and other forms of tetrahydrocannabinols commonly lead to cyclic vomiting that mimics bulimia.

Parorexia is an abnormal desire for certain substances, such as the craving for salt in uncontrolled Addison disease or for chalk in calcium deficiency states. The desire in early pregnancy for sour foodstuffs or other selective and often unusual foods is another example. Its mechanism is incompletely understood.

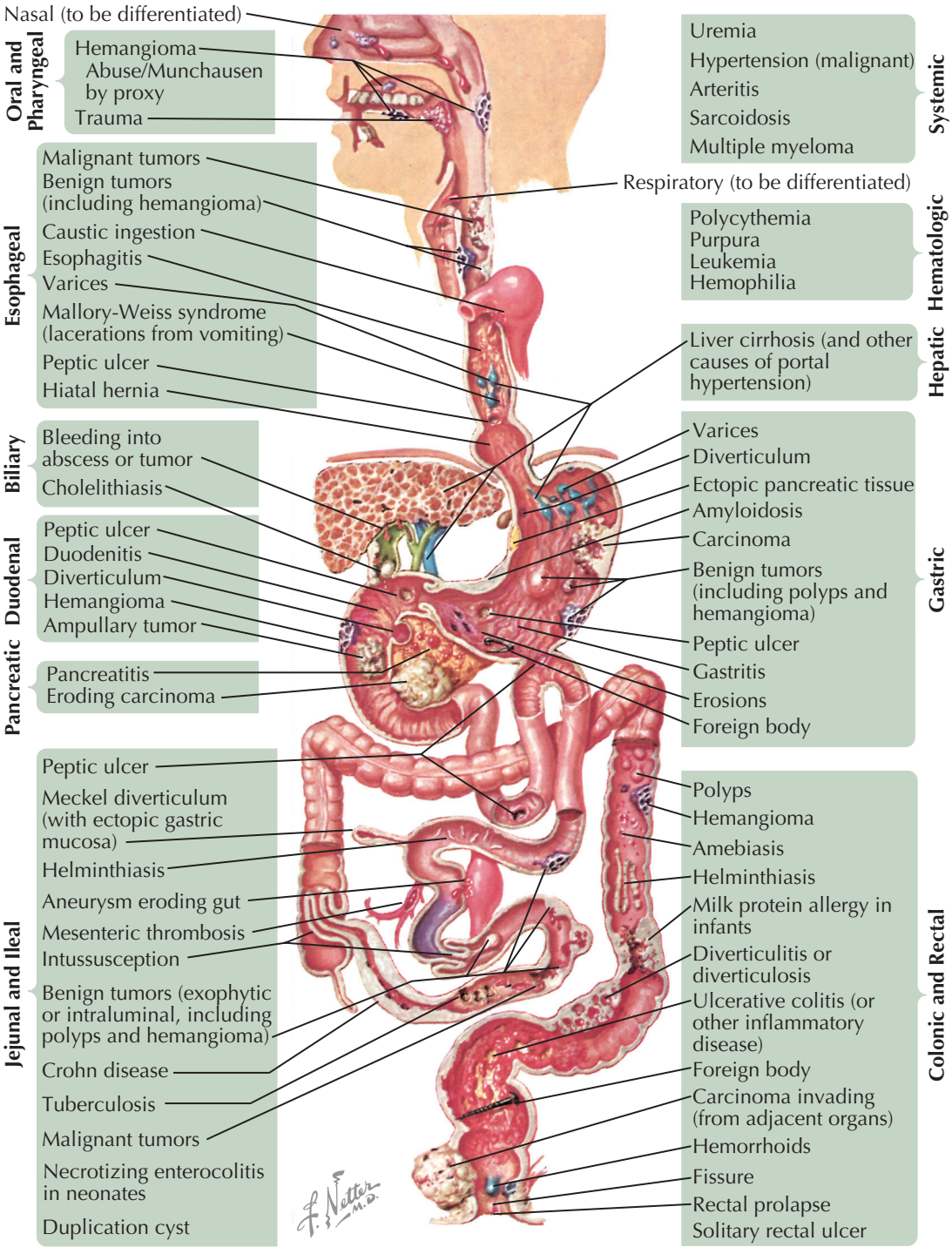
OVERVIEW OF
GASTROINTESTINAL BLEEDING

Bleeding is a common symptom of both benign and malignant disorders of the digestive system. Bleeding, even in the absence of other digestive tract symptoms such as pain, obstruction, or signs of perforation, always warrants a definitive evaluation because it may lead to a life-threatening loss of blood and is often associated with significant and/or potentially lethal disorders. The more evidence there is of bleeding (anemia, iron deficiency, or overt bleeding) the greater the likelihood that a serious disorder is present. Advanced malignancies are common causes of bleeding, but most causes are benign and treatable with medication and/or endoscopic techniques.

Evaluation of the cause of bleeding includes consideration of the location of gastrointestinal bleeding; one must also assess the severity and rapidity of blood loss. Blood loss from the digestive tract is described as overt when there is obvious bleeding and occult when bleeding can only be detected by stool testing, a drop in hemoglobin, or iron deficiency.

Overt bleeding from the upper digestive system presenting as the vomiting of bright-red blood is *hematemesis*. Partially digested blood that has turned black appears in vomitus as black strands of mucoid material or small specks of black described as *coffee ground emesis*. Bright-red blood expelled from the rectum is *hematochezia*. Passage of black stool from overt bleeding is *melena*, which has a distinctive odor well known to gastroenterologists and emergency physicians as an urgent call for prompt intervention. Hematochezia may be seen as droplets or staining of the toilet paper when it originates from rectal cancer or hemorrhoids, or it may fill the toilet bowl. In either situation, endoscopic diagnosis of the cause is necessary.

Bleeding is often not recognized until a patient is found to be anemic by physical examination or laboratory tests. Iron deficiency in males of any age and all nonmenstruating females is commonly due to bleeding. Although iron deficiency in premenopausal women is more commonly due to menstruation, gastrointestinal bleeding should always be considered. Malabsorption is also a common cause of iron deficiency. This is particularly common in patients with celiac disease and chronic gastric hypochlorhydria whether due to severe atrophic gastritis or to chronic use of high-dose proton pump inhibitors. Differentiating occult bleeding from malabsorption is facilitated by point-of-service stool testing for blood with paper tests that react to the presence of any oxidating substance (*stool guaiac test*) or immune reactions (*fecal immune test for hemoglobin*); the latter test is much more specific but less sensitive for upper gastrointestinal sources and more expensive. When blood



is found, a diagnosis should always be sought. Distinguishing between occult bleeding and malabsorption is difficult because bleeding from most lesions is intermittent. For example, in patients with known colon cancer extensive enough to require surgical resection, only one in four stool tests for occult blood will be positive. The limited sensitivity of these tests necessitates repeating stool examinations in four to six specimens 2 or 3 days before one can be confident there is no active bleeding. Repeat testing of stools, hemoglobin levels, and iron levels; keen judgment; and close follow-up are necessary when evaluating patients with suspected occult bleeding.

The most challenging patients are those who have documented bleeding but for whom a definitive cause is elusive. The term *occult gastrointestinal bleeding* is used

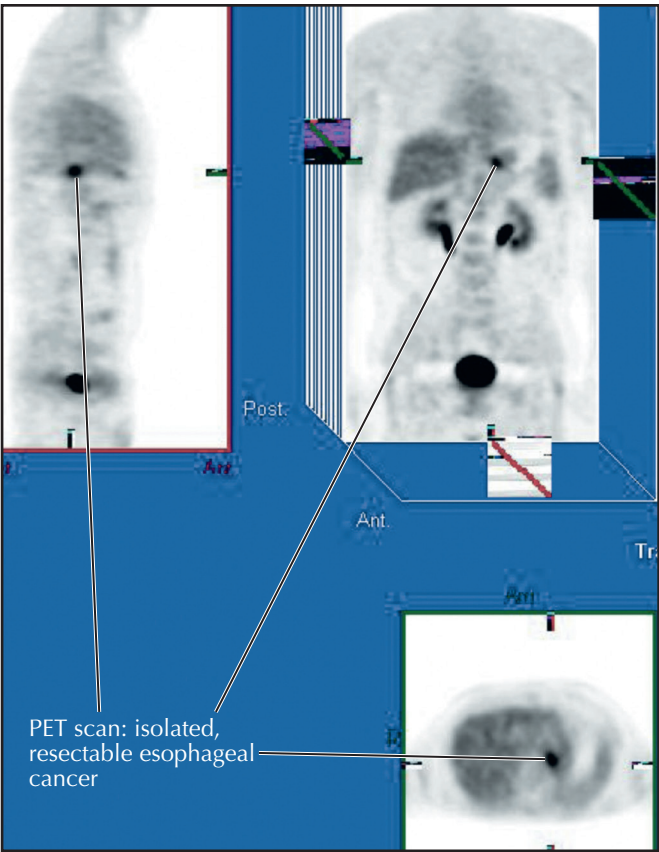
to describe such patients, including patients who have had a high-quality evaluation with both endoscopy and a well-prepped colonoscopy by an expert. When obscure bleeding is finally diagnosed, it is usually found by endoscopy or colonoscopy, because lesions may be intermittent or even lead to bleeding in the absence of an obvious break in the mucosa, as occurs with *Dieulafoy lesions*. If endoscopy and colonoscopy results are negative, techniques must be used that extend beyond the reach of these standard procedures, including capsule endoscopy, push enteroscopy, or single- or double-balloon enteroscopy. Radiographic tests that may be of value in the evaluation of such patients include nuclear medicine bleeding scans, angiography, and cross-sectional imaging with computerized tomography (CT) scanning.

DIAGNOSTIC AIDS IN GASTRIC DISORDERS

Every diagnostic evaluation must begin by taking a skilled history and performing a physical examination, but additional aids are usually necessary to make a definitive diagnosis that will provide a specific plan for effective treatment. Following the history and physical examination, laboratory testing and noncontrast chest or abdominal radiographs are often obtained. Common radiographic findings on plain x-rays (no contrast agent administered) for common upper digestive disorders are shown. The value of more precise imaging technologies with endoscopic and radiographic studies is discussed with Plates 1-61 to 1-64 and of breath testing with Plates 1-65 and 1-66. An important element of a thorough physical examination of a patient with symptoms of a digestive disorder is evaluation of the stool for blood. Detecting blood from the upper gastrointestinal tract using fecal occult blood testing with a guaiac-based technology, while less specific, is more sensitive than fecal immune testing for hemoglobin because the immunogenicity of a hemoglobin molecule released in the esophagus or stomach can be degraded by pancreatic and small intestinal digestive enzymes.

Physiologic testing of acid production and exposure and of motility functions of the upper digestive tract is a commonly used, invaluable tool. Three types of esophageal and gastric pH monitoring are in common use. The traditional esophageal pH study provided only a transnasal 24-hour study of reflux. It is time honored and safe and provides accurate information about the severity of exposure of acid in both the esophagus and stomach. Alternatively, an *intraesophageal clip pH study* can be performed by placement of a pH electrode 5 cm above the gastroesophageal junction using endoscopy. It has several advantages over the transnasal probe because it is wireless and therefore does not have the inconvenience, embarrassment, potential risk, and discomfort of the transnasal device. It records, for 48 hours, the intraesophageal pH measures as the patient eats and sleeps as usual; this can be a challenge with the transnasal device. The major disadvantage of both devices, however, is that pH recordings only report the severity of acid reflux. A major advance over both of these techniques is *high-resolution manometry* and the impedance reflux study. High-resolution manometry is performed with a probe that has multiple recording electrodes, permitting a more rapid and accurate evaluation of esophageal motility testing throughout the length of the esophagus, without the annoyance of moving the device. More importantly, the impedance technology permits the evaluation of both acid and nonacid reflux and fluid dwell time and a correlation between manometry and bolus transit. This device is limited by recording for only 24 hours and by placement of the catheter transnasally, but the increased accuracy and extensive diagnostic information provided coupled with the very small diameter of the device make it the procedure of choice for esophageal motility and reflux studies.

Physiologic testing of gastric motility and pH physiology are also commonly performed. Gastric motility is most commonly evaluated after a patient has eaten a meal of radio-labeled liquids and solids in the nuclear medicine department of a hospital or an outpatient



Diagnostic Findings of Upper Gastrointestinal Disorders on Plain Chest or Abdominal Radiographs		
Chest radiograph	Esophageal perforation	Mediastinal or cervical interstitial air, air-fluid level in an abscess
	Esophageal diverticulum	Air-fluid level, often epiphrenic or in cervical region (Zenker diverticulum)
	Esophageal cancer	Widened mediastinum, elevation of the left hemidiaphragm, malignant pleural effusion
	Achalasia	Interstitial pneumonitis, mid-chest air-fluid level, widened mediastinum, absence of gastric air bubble
	Mycobacterial infection	Calcified mediastinal lymph nodes, other evidence of tuberculosis in the lung
	Foreign body	Presence of density in posterior mediastinum or epiphrenic area
	Severe GERD	Aspiration pneumonia, particularly of the right mid-lung, interstitial lung disease
Abdominal radiograph	Gastric perforation	Free air under the diaphragm, particularly when not accompanied by an acute abdomen
	Outlet obstruction	Enlarged silhouette of air-fluid level in the stomach
	Foreign bodies	Coins, batteries, other swallowed foreign substances

facility. The test involves little radiation, is easy to perform, and has essentially no risk for the patient. The wide variability in normal emptying rates may affect the results, however, as may a patient's mood and overall health, which may also cause emptying times to vary widely (poor reproducibility). This has led to the recommendation that recordings be made for a minimum of 4 hours and that a standardized meal be eaten. Alternatively, gastric motility functions can be evaluated, along with small bowel motility, by means of a *capsule*

motility test. The capsule can be swallowed by a patient in the office, and recordings are made as the patient goes about normal activities. Gastric secretory physiology is most commonly evaluated by a basal rate and then by a stimulated, titratable gastric secretory rate. This test is very important in the evaluation of acid secretion in patients who may have Zollinger-Ellison syndrome or other causes of *hypergastrinemia*. Gastric acid secretory studies are described in greater detail with Plates 4-27 and 4-36.

UPPER GI IMAGES

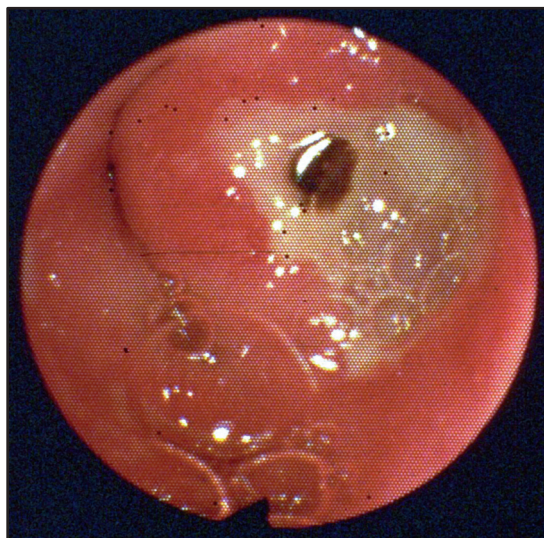
OVERVIEW OF IMAGING OF THE UPPER GASTROINTESTINAL TRACT

Even after a careful history and physical examination, imaging of the gastrointestinal tract is often required to make the correct diagnosis. Risk factors involved and the cost-benefit ratio should be taken into consideration before proceeding with imaging in lieu of prolonged careful observation or a therapeutic trial. The presence or absence of “alarm signs and symptoms” can aid this decision, including weight loss, nausea, vomiting, fever, age over 45, and evidence of bleeding, including a positive test for occult bleeding, gross bleeding, or anemia. Having particularly severe or worsening pain should increase consideration of further testing, as should pain that does not respond to simple measures or that interrupts sleep. Imaging the upper digestive organs can be achieved by endoscopic or radiographic techniques. Endoscopic evaluation is often the procedure of choice.

Radiographic testing includes noncontrast x-rays, contrast fluoroscopic testing, and cross-sectional imaging. Cross-sectional imaging of the chest, esophagus, and upper digestive tract is performed most commonly with CT scans. Other commonly used cross-sectional imaging technologies include magnetic resonance imaging (MRI) and positron-emission tomography (PET). These techniques are best suited for examining lesions in the wall of the digestive tract, liver, or pancreas or when there is suspicion for lesions extrinsic to the lumen. Arteriography is a commonly used diagnostic and therapeutic radiographic study valuable for evaluating tumor invasion and the site of bleeding. Therapeutically, it is used to treat persistent bleeding sources, to embolize, to deliver chemotherapy to malignant lesions, or to repair surgical anastomotic strictures.

Ultrasonography, with or without Doppler studies of blood flow, is a very valuable means of evaluating the liver, gallbladder, and pancreas and, in selected patients, the intestines. It is rarely of value, however, in examining the esophagus, stomach, or duodenum. Ultrasonography performed by a specially trained endoscopist is the procedure of choice for diagnosing intramural lesions and for staging tumors of the lung and gastrointestinal tract for possible mediastinal or celiac nodes.

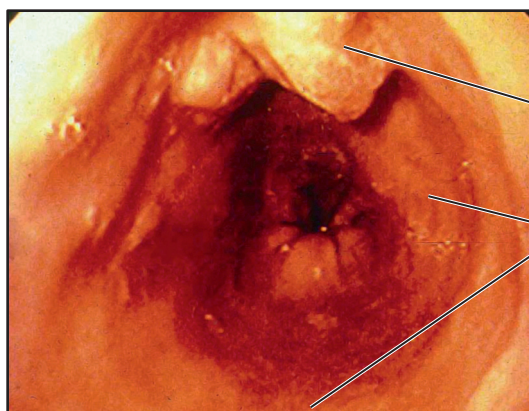
Plain, noncontrast imaging of the abdomen and chest can provide valuable diagnostic information in selected esophageal and gastric disorders. A plain film of the abdomen, often described as a flat plate or image of the kidney, ureter, and bladder (KUB), can be useful in the evaluation of intestinal gas or pancreatic calcification. The addition of an upright film of the abdomen and chest is often ordered as part of an obstruction series. Delayed gastric emptying is suggested if the gastric image is pronounced, but a definitive diagnosis will require additional studies. Achalasia should be considered when the chest x-ray shows a widened mediastinum with an air-fluid level and no gastric air bubble. If a perforation is suspected, an obstruction series is urgently needed and is essential to look for mediastinal air or free air under the diaphragm in the upright films. An obstruction series, including neck and chest x-rays,



Endoscopic image of small clot within a small duodenal ulcer (“red spot”).



High stricture of esophagus demonstrated by barium swallow.



Barrett adenocarcinoma seen endoscopically in distal esophagus.

Cancer

Barrett

should also be the first step in the evaluation of a patient with suspected foreign body ingestion. In both situations, however, if these films are negative but suspicion is high for a perforation or persistent foreign body, further cross-sectional imaging with a CT scan should be performed before barium or endoscopic studies are performed.

CONTRAST IMAGING OF THE UPPER GASTROINTESTINAL TRACT

Because most disorders of the upper digestive system are epithelial in origin, the most common imaging studies ordered for evaluation of the esophagus or stomach are fluoroscopic x-ray contrast studies or

endoscopic studies. The professional fee for each is similar, but the associated technical fees are high for both, vary greatly from ambulatory settings to hospital settings, and should rarely be used to determine which study to choose. Contrast studies have no risk except in a patient with an underlying perforation (see below). Contrast fluoroscopic tests must be performed in a radiology department, so a patient must be able to be transported to that area. The patient must be able to swallow or have a nasogastric tube and should be able to cooperate with the radiologist's efforts to position the patient. Contrast radiography is in some respects an art, and its accuracy depends considerably on the operator's skill.

When ordering fluoroscopic radiographic imaging, one must determine which swallowed contrast material

OVERVIEW OF IMAGING OF THE UPPER GASTROINTESTINAL TRACT (Continued)

is to be used. Barium should always be the contrast agent of choice when there is concern about the risk for communication between the digestive tract and the airway, either with aspiration or by fistula. Use of a water-soluble contrast agent such as gastrografin in such circumstances could lead to sudden pulmonary edema and bronchospasm, with dire complications. In contrast, water-soluble contrast such as gastrografin should always be used first to evaluate the esophagus or stomach for the presence of a perforation. Barium leaking into the chest in esophageal perforation or the abdomen in gastric perforation is very difficult to remove and may later serve as a nidus for infection. Techniques used add air to create a double-contrast image and markedly increase the accuracy of the examination.

Contrast imaging of swallowing disorders is particularly valuable when transfer dysphagia is considered or when a lesion in the neck or high in the esophagus is suspected.

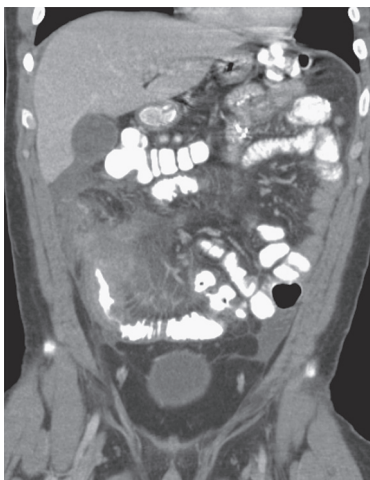
CROSS-SECTIONAL RADIOGRAPHIC IMAGING OF THE UPPER DIGESTIVE TRACT

CT scans are invaluable in the evaluation of unexplained pain, liver lesions, pancreatic lesions, and lesions that extend from or into a luminal organ. This includes thyroid, lymphatic, vascular, or lung lesions impinging on or invading the esophagus. Organs adjacent to the stomach and duodenum can impinge onto these upper gastrointestinal organs or be invaded by disorders originating from them, including the aorta, kidney, pancreas, gallbladder, and liver. CT scanning is also invaluable in the evaluation and staging of most cancers.

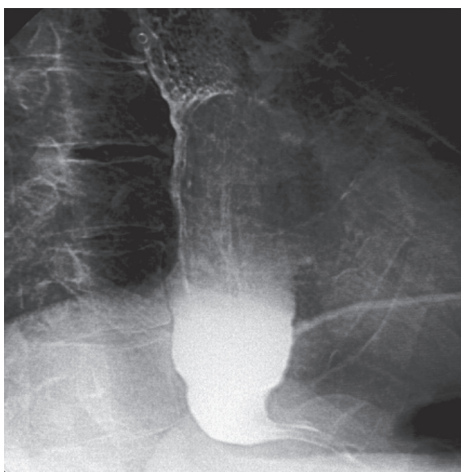
MRIs are more accurate in characterizing vascular lesions, including aneurysms, and tumors invading arteries and veins, including epithelial and stromal tumors, for staging of cancers and determining whether they are surgically resectable. MRI can also provide highly accurate images of the biliary tree and pancreatic duct (magnetic resonance cholangiopancreatography [MRCP]).

PET scanning is a functional imaging technique similar to CT scanning that uses various short-lived radioactive tracers, most commonly fluorodeoxyglucose. The radiation exposure is similar to that of CT scans. PET scans are often able to identify metastatic lesions that are missed or incompletely characterized by CT or MRI studies.

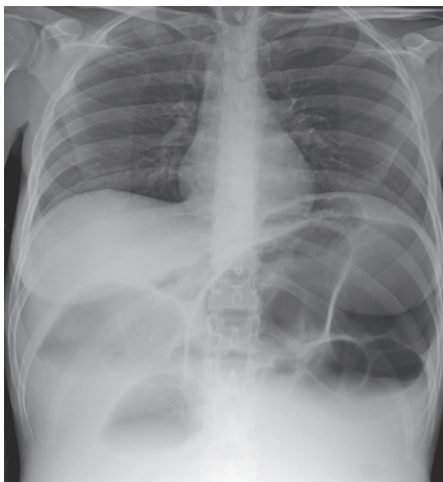
All three cross-imaging techniques require transporting the patient to the device and variable levels of patient cooperation. This is not an issue for ambulatory patients, but it becomes a major issue and risk to patients who are severely ill, particularly those in an intensive care unit. The patient must lie quietly and be able to tolerate being moved into the confined space of the circular device. CT scans and MRIs are often of greatest value when viewed with intravenous contrast, which also adds risk. Iodinated contrast agents are used in CT scans to differentiate vascular structures. When used in timed infusions, they can differentiate the rapid-



Plain radiograph (pseudoobstruction)



Barium swallow (achalasia)



Computed tomography scan (Crohn disease)

ity of filling times and differences in appearance with and without contrast and in the venous phase. Iodinated contrast poses a substantial risk, however, of causing renal dysfunction, particularly in patients with underlying renal disease, diabetes, uncontrolled hypertension, or dehydration. Patients are also commonly allergic to these dyes. A history of allergic reaction to shellfish or to previously administered dyes must be obtained because, although the reaction is most commonly manifested by a rash, it can lead to anaphylaxis. Oral contrast material does not carry any of these risks but can only be used in patients who can swallow effectively or who have a nasogastric tube. CT scanning is usually ordered only rarely in a patient's lifetime, but some patients undergo multiple scans. There is concern that such

repeated x-ray exposures increase the risk for neoplasms, particularly in younger patients. Such cancers do not develop for many years, or even decades, so the magnitude of the risk is incompletely understood.

MRI does not carry a risk for renal injury or neoplasm. Gadolinium-based contrast used in MRI enhances the value of the study by improving images of the vascular structures. This contrast can rarely cause a serious skin injury known as *nephrogenic systemic fibrosis*, particularly in elderly patients or patients with impaired renal function. During the MRI, the patient passes through a ring; this may be problematic for patients who are claustrophobic or morbidly obese. Open MRIs can be ordered for such patients, but with a sacrifice in accuracy.

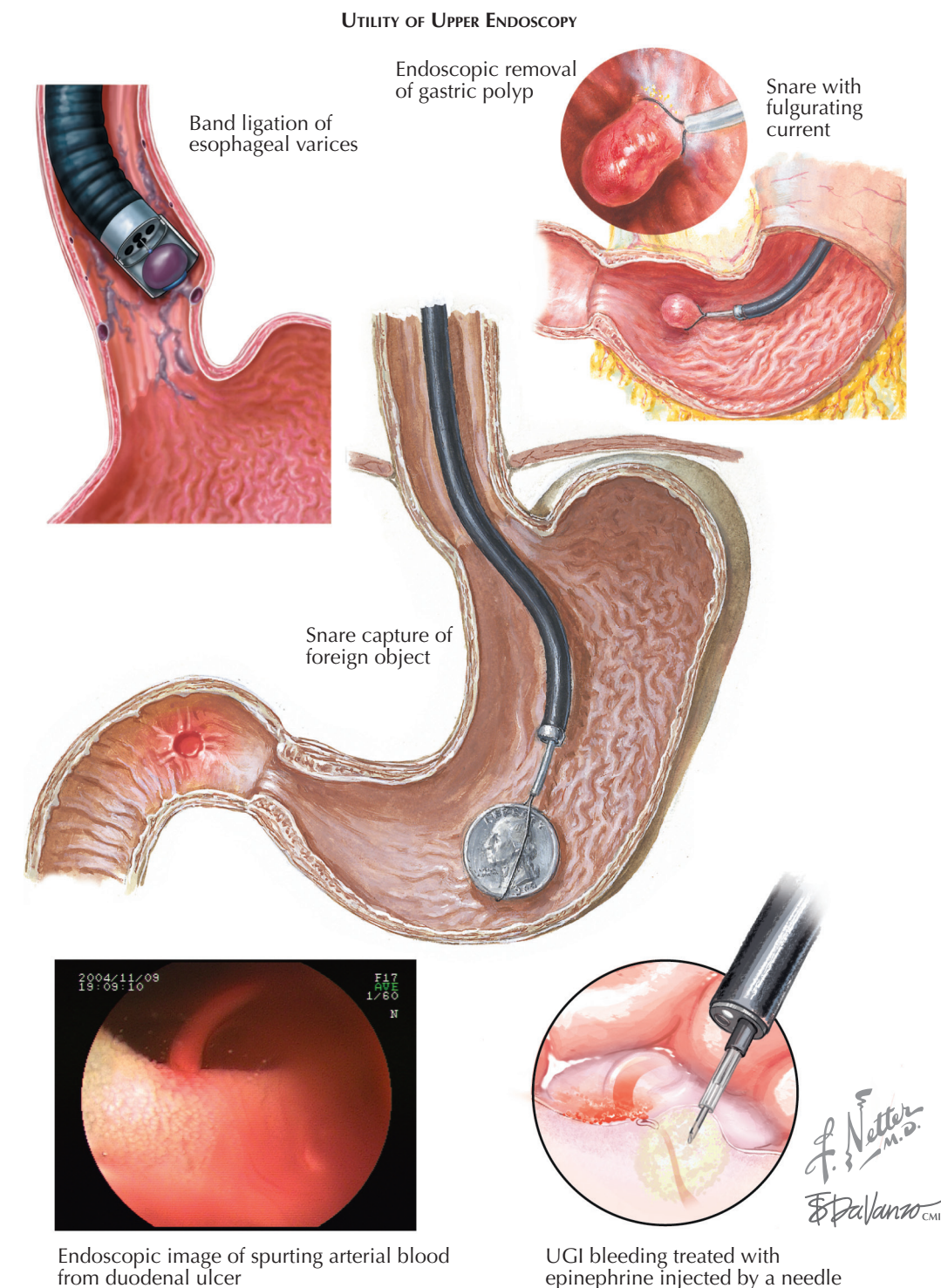
ENDOSCOPIC EVALUATION OF THE UPPER DIGESTIVE TRACT

Because of the increase in comfort, safety, and accuracy of endoscopic examination, it has replaced barium studies as the procedure of choice for evaluating the esophagus, stomach, and small intestine and colon. Upper endoscopy is very accurate and is considered the “gold standard” diagnostic test for most luminal upper digestive tract disorders. Barium contrast fluoroscopic x-ray studies are highly operator dependent and limited in quality in the best of hands. For example, barium contrast studies will be able to diagnose fewer than 65% of the causes of upper gastrointestinal bleeding (and therefore are contraindicated in such situations). Endoscopy can be performed in an ambulatory setting and anywhere in the hospital, permits the taking of pathologic specimens, and may be used to perform therapeutic interventions. Nearly all patients prefer to be sedated or even to be given monitored airway control heavy sedation, but such comfort measures are not essential for all patients and are not provided in all countries. The ordering physician must know when to use barium contrast studies performed by a radiologist and when to use endoscopy.

It is important for the clinician ordering endoscopic procedures to understand their special uses and quality metrics and the advantages and disadvantages of barium studies compared with endoscopic studies. Although it is technically the more invasive diagnostic test, endoscopy is perceived as being more comfortable because it is performed with sedation, and, therefore, it is much preferred by patients. Endoscopy is also preferred because it is much more accurate and permits the taking of specimens for cytologic, microbiologic, or pathologic assessment. It is also used to perform a wide variety of therapeutic procedures. If appropriate, this invaluable tool can be brought to the bedside of the sickest patients in the hospital's intensive care unit for both diagnostic and therapeutic interventions. In contrast, all radiologic studies require the transportation of the patient to the specialized x-ray equipment located in the radiology department of the hospital, except for the simplest of plain x-rays and ultrasound studies. This section will briefly describe the process of upper endoscopic procedures and the use of three upper gastrointestinal endoscopic procedures, endoscopy, endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasonography (EUS). The ordering physician must appreciate when to use these studies and the potential risks and quality metrics to look for in the results.

PREPARATION AND SEDATION TECHNIQUES

Ensuring the patient's safety is of the highest priority in endoscopy. One must ask if the procedure is clearly indicated, whether this is the safest approach to getting the diagnosis or treatment, and whether this is the optimal time in the course of the patient's illness to perform the procedure. Cardiac, pulmonary, and coagulation studies are not usually indicated, but they may be needed in select patients who have unusual risks. The endoscopist must be aware of all underlying medical conditions, all prescribed and over-the-counter medications taken, and any concerns about the coagulation status. If possible, anticoagulants should be held if intervention is anticipated, but this is not always pos-



sible or prudent. Knowing the status of the patient's platelet count and coagulation tests is imperative if one has any reason to suspect they are abnormal, especially if intervention is planned. If the patient has an active cardiac or pulmonary condition, including obstructive sleep apnea, the patient must be assessed, if necessary by a cardiac or pulmonary specialist. Because morbidly obese patients are particularly at risk, office endoscopy is not recommended for them, and they may require preprocedure assessment.

Once the procedure has been scheduled, the patient must be aware of her or his responsibilities. One of the most common severe complications from upper endoscopic procedures is aspiration pneumonia. Except in select cases, the procedure is performed without

protection of the airway by intubation. Thus the patient must have taken no food by mouth for at least 6 hours and no clear liquids for at least 2 hours. Of course, these standard times for fasting should be longer in patients at high risk for aspiration, including those with achalasia and gastric emptying disorders. Special instructions should be given to patients regarding their blood pressure and diabetic medications. In patients with active bleeding, the blood pressure and pulse should be made as normal as possible by crystalloid fluid and, if necessary, blood resuscitation. Before starting the procedure, time should be taken to ensure that all providers and nurses are aware of the patient's risk factors, including allergies, risks of the procedure to be performed, and risks of any intended interventions.

ENDOSCOPIC EVALUATION OF THE UPPER DIGESTIVE TRACT
(Continued)

ENDOSCOPY AND ENTEROSCOPY

Endoscopy is generally a very safe test and can be performed in nearly all patients with ease and no anticipated ill effects within 5 to 15 minutes (or longer if interventions are performed). It can provide highly accurate imaging of the entire upper digestive system to the distal duodenum or, if enteroscopy is performed, well into the jejunum or ileum. Histologic, microscopic, or cytologic specimens increase the diagnostic accuracy with negligible risk. Interventions are commonly performed with endoscopy, including dilations of the esophagus or duodenum, the placement of stents to treat resistant strictures or cancers of the esophagus or duodenum, and the placement of feeding tubes. The key to quality is adequate analysis of all parts of these organs with photo documentation and the taking of a sufficient number of biopsies in accord with published guidelines. It has been shown that the errors of upper endoscopy occur when sufficient time is not taken to examine parts of structures that are challenging to see clearly or to achieve a thorough evaluation. This includes examining all of the esophagus; documenting the site of the squamocolumnar junction; examining in detail the fundus in a retroflex view; examining the angularis, pylorus, and all parts of the bulb of the duodenum; and reaching at least the third part of the duodenum. The guidelines for diagnosing specific upper gastrointestinal disorders should be understood by the ordering physician (see Sections 2 to 4). For example, one should obtain at least six biopsy specimens throughout the esophagus to rule out eosinophilic esophagitis, nine specimens of gastric ulcers to rule out malignancy, and six specimens of the duodenum, including two in the bulb region, to rule out celiac disease.

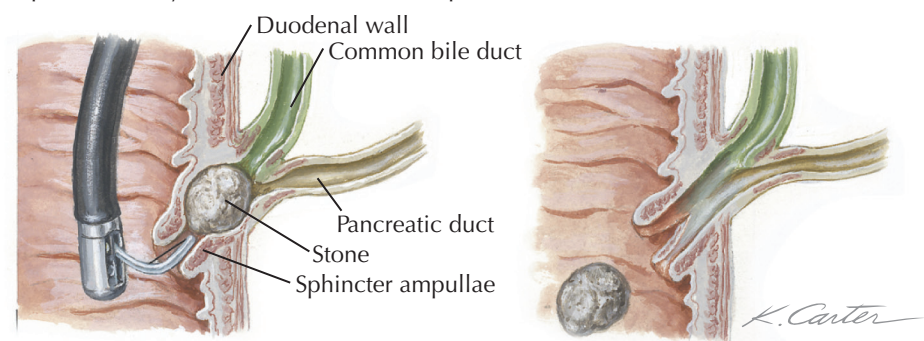
ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

ERCP will be discussed at length in the chapter on biliary disorders. Only very highly skilled endoscopists perform this procedure, usually after a fourth year of training or many years of experience. It can often provide therapeutic intervention that avoids major surgery, including bile duct stone extraction and ductal stenting. Diagnostic ERCP has rarely been indicated since EUS and MRCP have become available, both of which can examine the bile duct and ampulla in detail with negligible risk. In years past, it was common to hear that the duct could not be cannulated, but in expert hands, this is now a rare occurrence. Because of its potential duration, this is the one upper endoscopic examination that may require preemptive planning for intubation and general anesthesia.

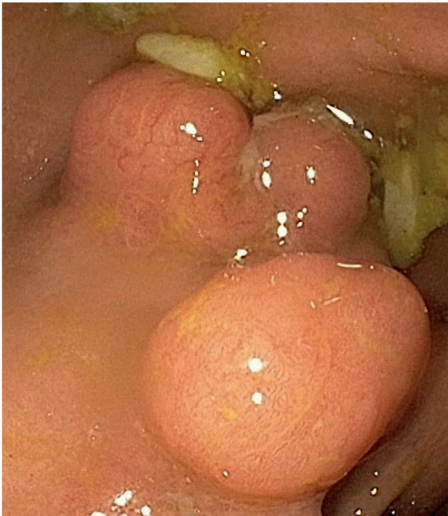
Endoscopic Ultrasonography

EUS is performed by endoscopists who are trained at length on its uses. The procedure is performed with an

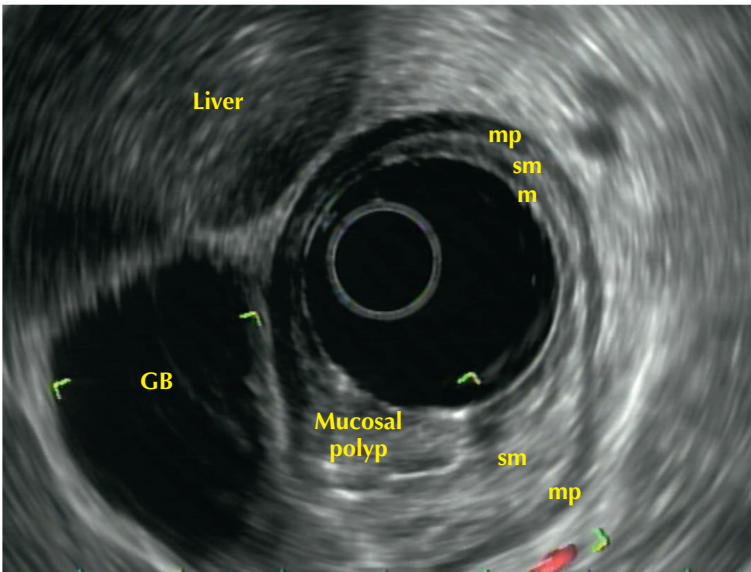
Sphincterotomy for release of stone in ampulla of Vater



Multiple large lesions found by endoscopy in stomach during evaluation for iron deficiency.



Endoscopic appearance did not clearly indicate whether larger lesions could be safely removed endoscopically.



Endoscopic ultrasound image clearly showed lesions to be limited to mucosa. All were safely removed and found to be benign but presumably premalignant adenomas.

endoscope that has been modified by the placement of one of several transducer types at the tip of the scope. It has become the procedure of choice to examine nodes adjacent to abdominal organs and the esophagus; the distal common bile duct; submucosal lesions and pancreatic lesions; and fluid collections. It is highly accurate for lesions that may be only millimeters in diameter because the transducer is placed directly on the lesion.

It also permits the collection of cytologic specimens by using fine-needle aspirates of the lesions and/or biopsies. In the setting of cysts or abscesses, EUS can be used diagnostically to collect intralesional fluid for culture, cytologic, or biochemical assessment or therapeutically to drain the lesion. It can also be used to guide an interventional procedure such as pancreatic cyst drainage by creating an endoscopic cyst gastrostomy.

HISTOLOGIC AND CYTOLOGIC DIAGNOSIS

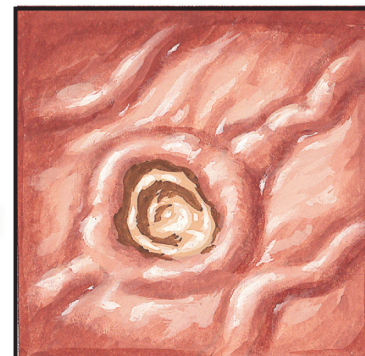
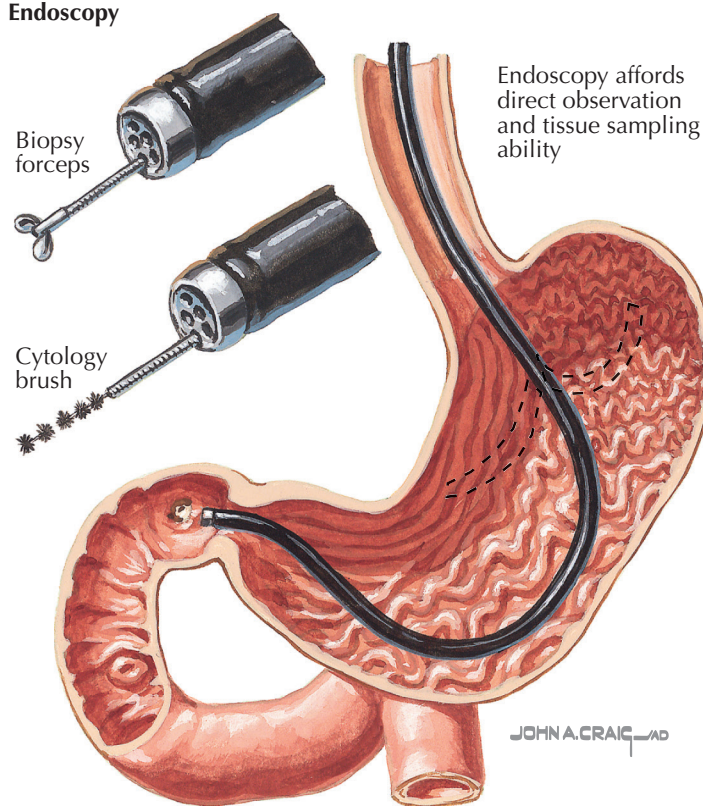
Safe, minimally invasive techniques have been developed to definitively diagnose most digestive disorders, including the acquisition of cytologic or histologic specimens. This has been particularly important in malignant disease, where it is rarely, if ever, acceptable to consider treatment without first making a “tissue diagnosis.” In many more cases, cytology or pathology obtained by endoscopy can exclude a malignancy or diagnose a malignancy that does not require surgical intervention (e.g., gastric mucosa-associated lymphoid tissue [MALT] lymphomas, which are treated with antibiotics; malignancies that are diffusely metastatic and therefore beyond the benefit of surgery).

In many situations, highly accurate photo documentation may be a most valuable tool in making the diagnosis and guiding therapy. Much more often, however, biopsies are essential, even at times when the gross appearance is normal. Common examples of this in the upper gastrointestinal tract include eosinophilic esophagitis and celiac disease. Histology can also determine the cause of what may appear to be mild nonspecific erythema to reveal that it is due to an infection or Crohn disease. Histologic specimens obtained by endoscopic biopsies or cytologic specimens provided by brushes or fine-needle aspiration provide the clinician with definitive data with which an effective therapeutic strategy can be designed.

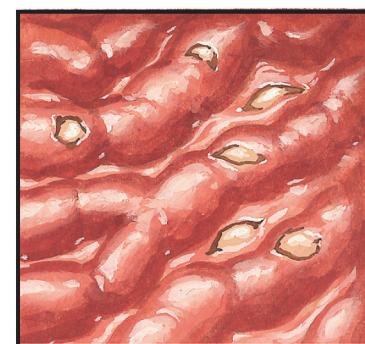
When receiving the results of a procedure, the ordering clinician should clarify whether biopsies or cytologic specimens were taken and the number of specimens taken. Providing the pathologist with a sufficient number of specimens to make a definitive diagnosis is a key quality metric. It is rarely, if ever, appropriate to take fewer than three specimens; taking this number does not increase the number of passes of the forceps (time) needed or the expense of the procedure. Endoscopists should also be adept at directing the biopsy forceps. Receiving an endoscopic report with photo documentation of an abnormality but with a pathology report that is read as normal should raise concern. The specimen should be taken with an optimal orientation. Taking biopsies tangentially to the orientation of the mucosa makes it difficult to provide a definitive and accurate diagnosis. Orientation is particularly important in the duodenum, where the biopsy should be obtained across a fold (plicae circulares) and perpendicular to the mucosa to accurately assess villous height and crypt depth, as is critical in assessing the diagnosis and severity of small intestinal mucosal diseases such as celiac disease.

Most exfoliated cytologic specimens are obtained by endoscopically guided brush cytologic procedures or interventional radiology experts. Abrasive brush devices for obtaining tissue for cytologic diagnoses, including an intraesophageal brush, have been proposed as a less invasive means of diagnosing esophageal disorders. Although the risk is lesser than with endoscopy, the procedure rarely provides definitive data for treatment and management. Potential limitations of guided fine-needle aspirations, whether obtained by EUS or radiol-

Endoscopy

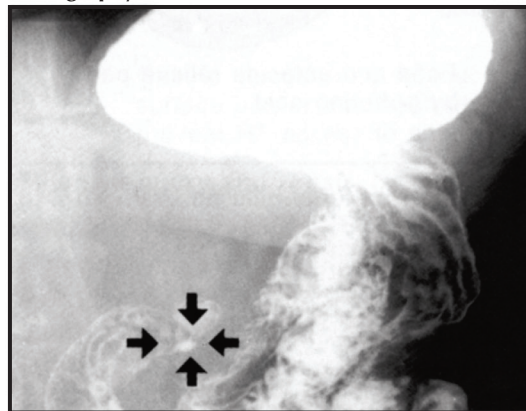


Duodenal ulcer

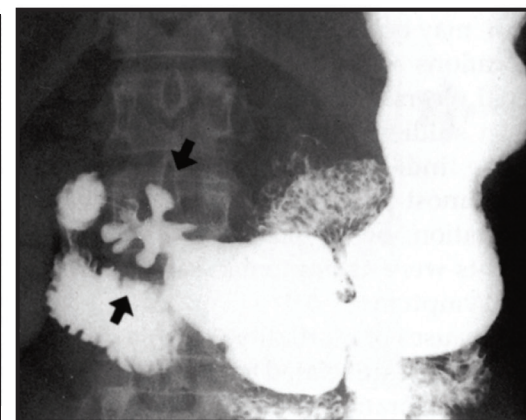


Gastritis with erosions

Radiography (barium examination)



Barium-filling ulcer crater

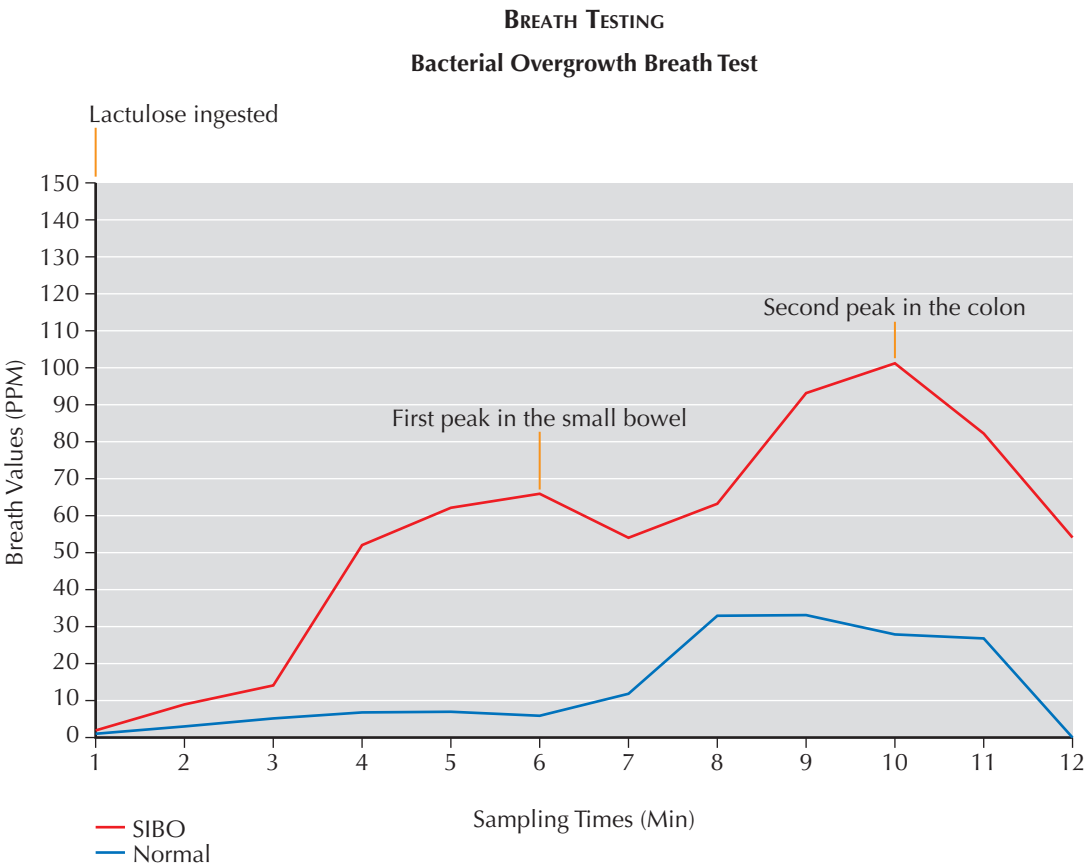


Deformed duodenal bulb

ogy, include the risk of discomfort or bleeding; even multiple passages of the needle may not provide adequate cellular data. The risk of inadequate cellular data can be reduced by having a cytology expert in the procedure room to assess the quality of such specimens.

The problem of being able to provide definitive histologic or cytologic information for guiding treatment occurs all too commonly with the myriad of functional gastrointestinal disorders for which no histologic or cytologic specimen can provide a definitive diagnosis. These disorders are particularly challenging because they are common, lead to substantial degradation in the quality of life, and lead to a loss of productivity and success at school or work, but they almost never lead to serious complications or shortening of the life span. The astute clinician must use judgment based on the

risk of finding an alternative diagnosis, particularly a life-threatening disease, to determine whether the taking of endoscopic photographs or histologic or cytologic specimens is warranted. To aid in this decision, various alarm signs and symptoms have been identified for most symptom complexes. These include symptoms that persist after effective therapy or that interrupt sleep; age over 45 years; the presence of fever, weight loss, nausea and vomiting, or anemia; or gross blood loss. Experts have also identified a number of criteria by which a diagnosis of a functional disorder can be made without ordering unnecessary testing, most notably the ROME criteria. Although they are not without controversy, such approaches provide a means by which excessive endoscopic and radiologic testing can be minimized.



BREATH AND STOOL TESTING

Testing exhaled breath or discharged stool can provide invaluable information in the diagnostic evaluation of disorders of the digestive system. Breath and stool testing can be performed at the point of service or can require more sophisticated biochemical or radiopharmaceutical analysis. Appreciating the spectrum and value of such tests enhances one’s diagnostic acumen.

BREATH TESTING

The number and uses of breath tests continue to be expanded. In ancient times astute diagnosticians reported the ability to detect disorders of digestion and the liver from the patient’s breath. A feculent odor of breath can be associated with achalasia, gastroparesis, small intestinal bacterial overgrowth, and partial small bowel obstruction. *Fetor hepaticus* is sometimes noted in patients with cirrhosis.

An excess of hydrogen concentration in the breath soon after ingestion of nutrients is used by gastroenterologists with greater precision than can be expected by olfaction alone to identify even mild disorders of small intestinal bacterial overgrowth. The same technology can be used to diagnose common disaccharide malabsorption problems with sucrose or lactose when these sugars are used as a substrate. Collection of radiopharmaceutical-labeled substrates can also be used to diagnose these and other malabsorption disorders.

Breath tests are widely used to diagnose the effectiveness of antibiotic therapy for *Helicobacter pylori*. These tests capitalize on the fact that these fascinating organisms can influence the pH of their environment within the gastric mucus layer by splitting ammonium ions. Tests of exhaled breath after the ingestion of C13-urea is standard for select patients for whom the presence

of this infection is clinically important. This includes patients who have had complications from *H. pylori* infection, such as complex peptic ulcers and MALT lymphomas.

STOOL TESTING

It is important for clinicians to be familiar with the most common stool tests, their strengths, and their limitations. As in all diagnostic evaluations, an evaluation of abnormal stool output should begin with a description of the stool being evacuated. It must be admitted that observing the consistency, color, and other factors of the appearance of the stool contributes only infrequently to the diagnostic information obtained by a carefully extracted history and the application of appropriate tests. Having stated that, it must be emphasized that the accurate description of stool color continues to have high diagnostic value. An *acholic stool* will certainly suggest biliary obstruction. A *tarry stool* indicates gastrointestinal bleeding, usually from the upper levels, and a *stool colored red with blood* means bleeding in the lower intestinal tract.

Although many descriptors have been considered excessive, attention to the appearance of the stool is rarely useful. Furthermore, patients often complain of increased stool odor, but all stool is malodorous. One widely used scale of stool appearance that has been validated is the Bristol Stool Scale. Using this scale can increase the objective assessment of the severity of disordered defecation and enhance the patient’s ability to communicate concerns.

The stool volume output over 24 hours should be determined in any patient with diarrhea that develops in the hospital or who complains of chronic diarrhea. In both settings, stool output is often normal. Hospital-

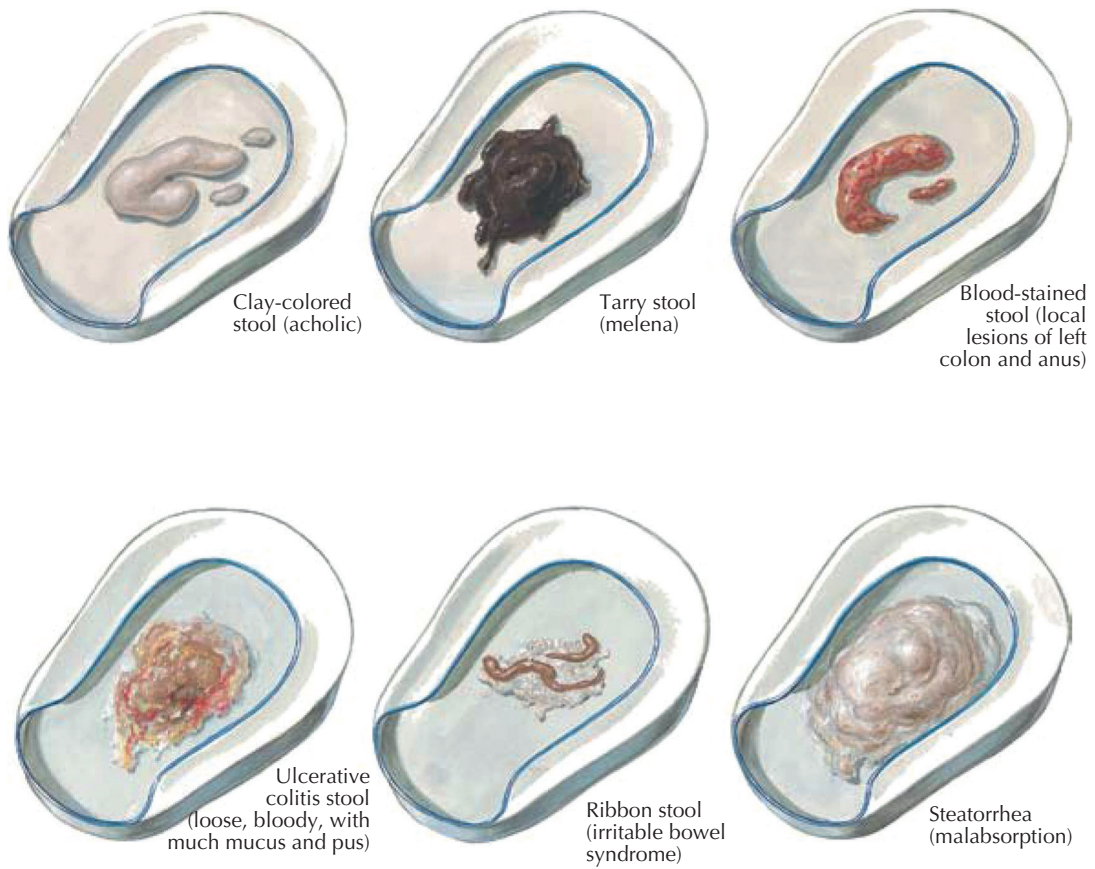
ized patients often complain of diarrhea when the problem is actually fecal incontinence. This may result from inadequate intake of fiber in the diet to produce formed stools, loose stools from medications, and deconditioning or illness that leads to weakness of all muscles, including those contributing to continence. Increased liquid or fecal incontinence may also be due to *paradoxical diarrhea*, in which there is frequent passage of small volumes. Patients with subacute or chronic diarrhea often suffer from altered bowel habits related to irritable bowel syndrome but do not expel more than 250 mL of stool necessary to make an objective diagnosis of true diarrhea. Quantifying stool output while the patient is fasting is also a very useful way of distinguishing diarrhea due to malabsorption (*osmotic diarrhea*) from diarrhea due to an inflammatory disorder, a secretagog, or surreptitious diarrhea.

The most common test of the stool is to determine the presence or absence of mucosal breaks leading to bleeding. Fecal occult blood tests and the fecal immune test for human hemoglobin have been reviewed in the section on gastrointestinal bleeding.

Patients suspected of having intestinal infections often undergo stool testing; most patients who develop new onset of diarrhea have an infection. The stool test for infection often begins by looking for fecal leukocytes (stool white blood cells). This test is positive when enteroinvasive, severe enterotoxic, and autoimmune enteritis or colitis is the cause. False-negative tests for fecal leukocytes may occur when stool volumes are very high or when the stool specimen is not collected as a fresh specimen, is not placed in preservative, or is contaminated by urine.

Specific causes for acute diarrhea can be determined by several mechanisms. Enteroinvasive bacterial infections are detected by culturing the stool. When *Yersinia*

STOOL TESTING



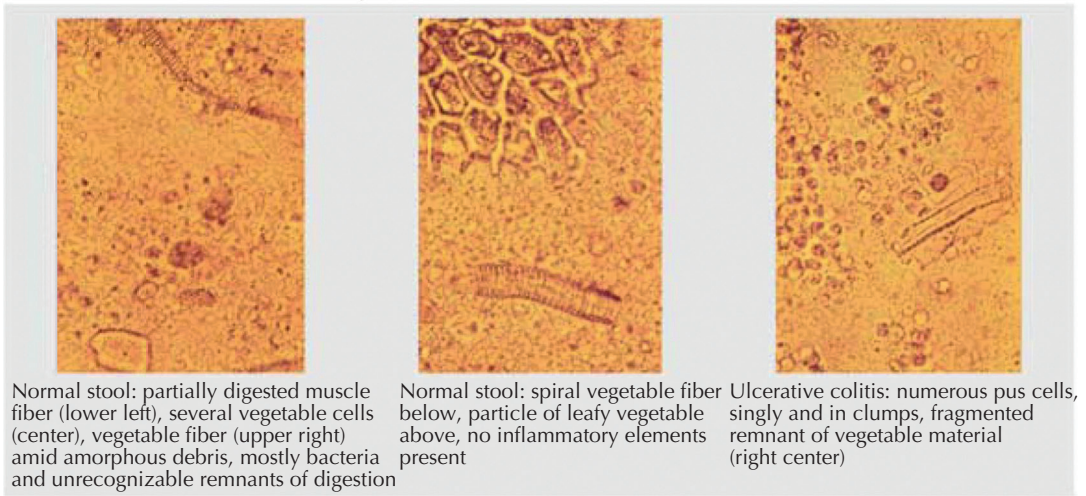
BREATH AND STOOL TESTING
(Continued)

colitis is suspected, special culture techniques should be requested using selective media such as MacConkey agar. DNA testing of specific virulence markers is also valuable for bacteria such as *Yersinia* and *Escherichia coli*, which are plentiful in the microbiota in nonpathogenic strains. Identifying the specific bacterial cause of diarrhea is important to direct antibiotic treatment and identify a specific carrier of transmission in epidemic infections. Helminthic infections and parasitic causes of acute diarrhea can be detected by expert microbiology technicians. False-negative tests are common, however, and fresh specimens should be evaluated three times to be certain that a test for ova and parasites is negative. A specific cause for infectious diarrhea often goes unidentified because most infections are due to viruses, toxins, or a strain of *E. coli*.

The presence of specific infectious agents can be detected by testing the stool for DNA to common pathogens or the toxins they release. This is most commonly performed to detect *C. difficile* superinfection in patients whose normal microbiota has been altered by antibiotics. Cultures can be used, but sensitive assays for toxin are the most rapid means of detecting this potentially lethal infection and in detecting if the most lethal form of the disease (NAP-1) is present.

Inflammation in the intestinal tract can be detected by identifying leukocytes or their by-products in the stool including lactoferrin, myeloperoxidase, or calprotectin. Blood tests such as sedimentation rate or C-reactive protein can also reveal gut inflammation, but erroneously normal results are not infrequently encountered.

Evaluation of chronic diarrhea should lead to a consideration of malabsorption. This should begin by collecting several stool specimens in ice and sending them to the laboratory to be evaluated for sodium and potassium and stool osmolality. When malabsorption is present, a correctly performed comparison of

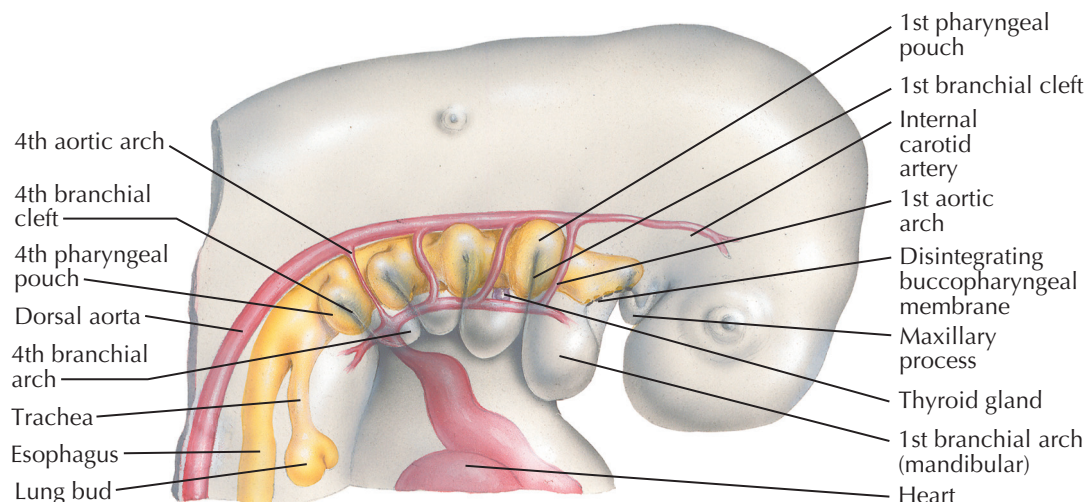


specimens will detect excess osmolality not explained by electrolytes alone (hyperosmolar). The specimen should also be tested for phenothalines and magnesium, indicating surreptitious laxative use, and for stool creatinine to rule out contamination by urine. Performing the test is not only unpleasant for the patient and nurse, it is technically challenging, because if it is not iced continuously, it will become uninteruptable because of

fermentation or steatorrhea caused by the complexity of mechanisms needed to absorb fatty nutrients into cells that primarily consist of water. Steatorrhea can be detected by using a qualitative Sudan stain slide or quantitatively by accumulating a 24-hour collection of all fecal output while the patient is on a 100-g fat diet. This is a difficult diet to follow and a very challenging collection to make.

MOUTH AND PHARYNX

Development of the thyroid and parathyroid glands



DEVELOPMENT OF MOUTH AND PHARYNX

The lining of the primitive gut tube is derived from the embryonic endoderm and the supporting tissues and mesentery from the visceral layer of lateral plate mesoderm. The amniotic cavity expands around the developing embryo to create the body wall but leaves the endoderm/ectoderm connection at the *oropharyngeal membrane* and caudally at the *cloacal membrane*. The early mouth, *stomodeum*, is formed by the ectoderm and the early pharynx by the endoderm. The developing pharynx is properly part of the foregut and it extends from the oropharyngeal membrane to the *respiratory diverticulum*. During the fourth week of development, the oropharyngeal membrane ruptures.

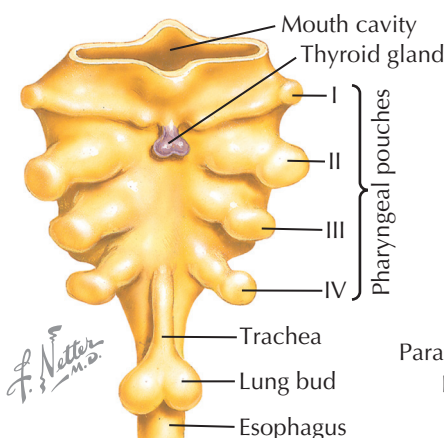
A large fold of mesenchyme located over the eventual forehead, the *frontonasal prominence*, extends inferiorly to form the superior border of the stomodeum. Two *maxillary prominences* are found on each side of it, and a single, fused *mandibular prominence* borders the stomodeum inferiorly. The frontonasal prominence develops two *nasal placodes* that hollow out to become the nasal cavities. On either side of the placodes are the *lateral* and *medial nasal prominences*. The lateral prominences fuse with the maxillary prominences to create the nasolacrimal grooves. The medial nasal prominences fuse with each other on the midline to form the philtrum of the upper lip and also with the maxillary prominences to create the upper lip. The medial nasal prominence also carries the mesenchyme that will differentiate into the primary palate, which fuses with the palatine processes of each maxilla to form the hard palate.

The pharyngeal (branchial or gill) arches are found on both sides of the developing neck. These arches consist of mesenchyme from neural crest cells, which form the connective tissue structures of the face and direct the formation of the other structures thereafter. Each arch contains a cartilage core, an aortic arch, a skeletal muscle, and a cranial nerve.

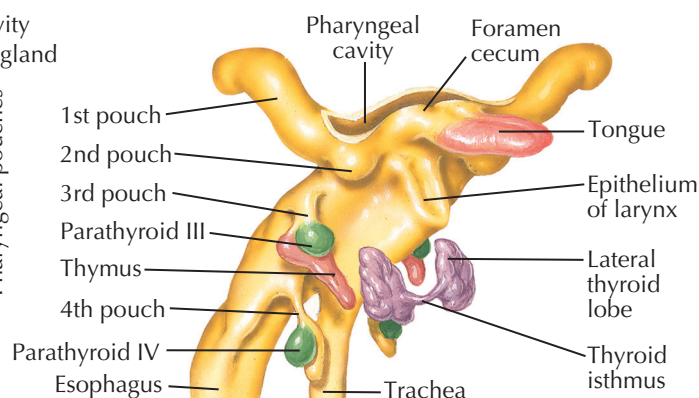
The *first pharyngeal arch*, which is supported by the *Meckel cartilage*, gives rise to the maxillary and mandibular prominences, mandible, incus, malleus, and other facial bones. The muscular mesenchyme therein is innervated by the trigeminal nerve, and it differentiates into all the muscles innervated by that nerve.

The *second pharyngeal arch* is supported by the *Reichert cartilage*, and it gives rise to the lesser horn and part of the body of the hyoid bone, styloid process, and stapes. The muscular mesenchyme in the second arch is innervated by the facial nerve, and it differentiates into all the muscles which that nerve innervates. The second arch, in conjunction with the first, will also form the *auricle* of the ear.

Pharynx (ventral view) 4th week



Pharynx and derivatives (between 6th and 7th weeks)



The cartilage of the *third pharyngeal arch* creates the remainder of the hyoid bone. The only muscle derived from it is the *stylopharyngeus*, which is innervated by the *glossopharyngeal nerve*.

The *fourth pharyngeal arch* gives rise to (most of) the thyroid cartilage. The vagus nerve innervates the muscle mesenchyme of the fourth arch, which will give rise to all the pharyngeal and palatine muscles apart from the *stylopharyngeus* (IX) and the *tensor veli palatini* (V3). The external branch of the superior laryngeal nerve (vagus) innervates the *cricothyroid* and *cricopharyngeus* muscles.

The fifth pharyngeal arch exists in some animals but not in humans. However, the *sixth pharyngeal arch* and its cartilages give rise to the rest of the thyroid and all the other laryngeal cartilages. The muscle mesenchyme in this arch is innervated by the *recurrent laryngeal nerve*, a branch of the vagus, which innervates the *intrinsic laryngeal muscles*.

The spaces between arches on the exterior of the neck form *pharyngeal grooves*, and those spaces on the interior side form *pharyngeal pouches*. The *first pharyngeal groove* is located between the first and second pharyngeal arches; it deepens toward the first pharyngeal pouch until only a thin membrane separates them. The *external auditory meatus* is the derivative of the first groove, and the *middle ear* and *auditory tube* are rem-

nants of the first pouch, with the tympanic membrane separating them.

The second, third, and fourth pharyngeal grooves fuse and migrate into the developing neck as they are overgrown by mesenchyme, briefly forming a *cervical cyst* that dwindles and disappears. The second pharyngeal pouch forms the bed of the *palatine tonsil* as lymphocytes migrate into its hollow, medial side. A dorsal extension of the third pouch forms the *inferior parathyroid gland*, and a ventral extension forms the *thymus*. Similarly, a dorsal extension of the fourth pouch forms the *superior parathyroid gland* and a ventral extension to the calcitonin-producing *C cells* of the thyroid gland.

The tongue forms in the anterior part of the developing mouth as two *lateral lingual swellings* and one *medial lingual swelling*, which enlarge and fuse. The muscles developing deep to these swellings are derived from somites innervated by the *hypoglossal nerve*. The lingual swellings are located in the floor of the first arch, and their surface lining is innervated by the mandibular branch of the trigeminal nerve. The rest of the tongue forms deep to the second, third, and fourth arches. A small diverticulum forms in the floor of the mouth between the second and third arches. This is the *foramen cecum*, and it will extend inferiorly and eventually separate from the tongue, travel along a pathway called the *thyroglossal duct*, and become the *thyroid gland*.

ORAL CAVITY

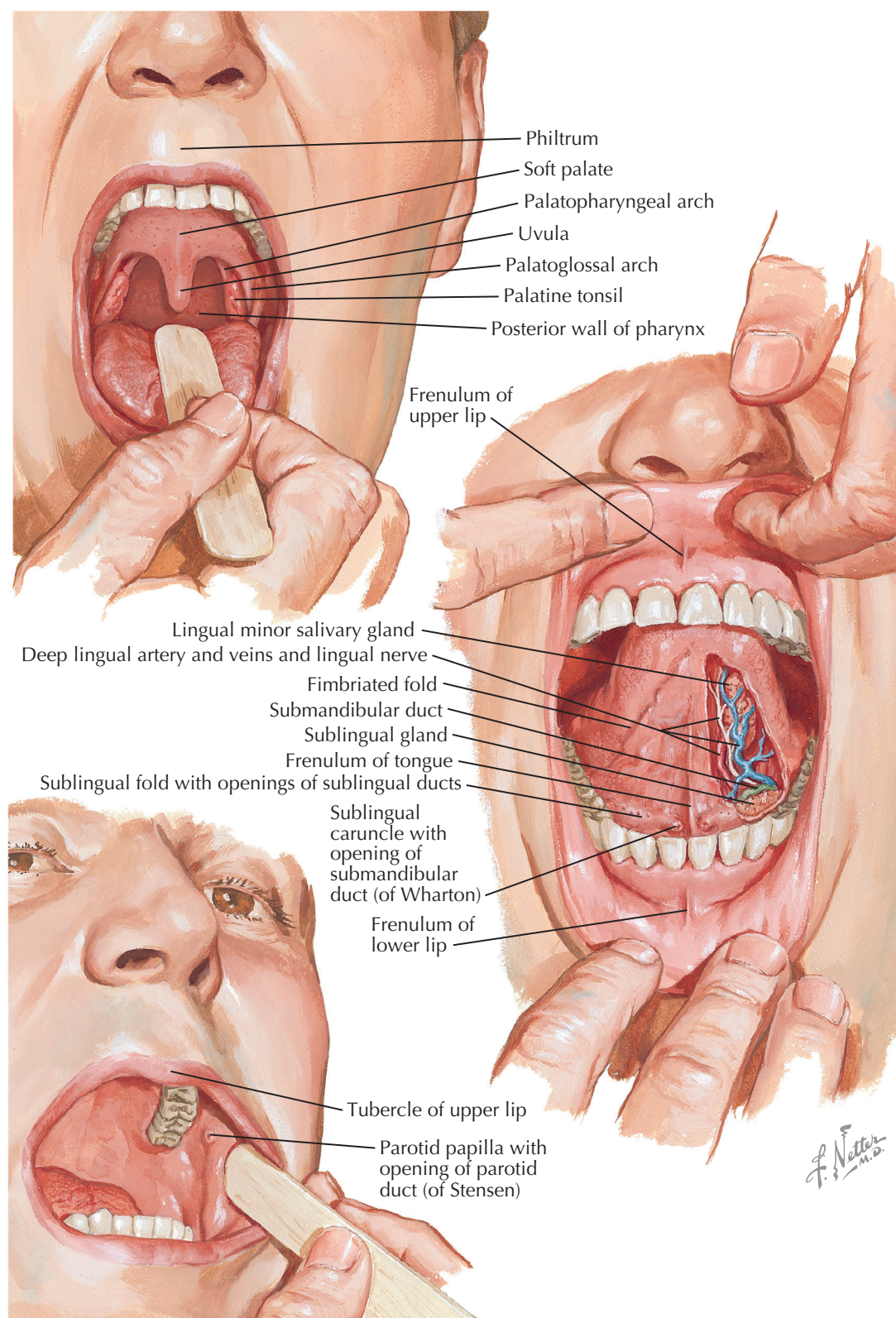
The mouth, or oral cavity, is the beginning of the alimentary canal. Its roof is formed by the palate, the tongue rises up out of its floor, and the cheeks and lips form its boundaries laterally and anteriorly. The mouth communicates anteriorly with the external environment by the rima oris, or oral orifice, and posteriorly with the pharynx through the isthmus of the fauces. The oral cavity is divided into the vestibule and oral cavity proper by the teeth and alveolar processes of the mandible and maxilla. When the mouth is closed, these two parts are connected only by the small spaces between the teeth and a variable gap between the last molar tooth and the ramus of the mandible, through which a catheter can be passed for feeding when the jaws are closed tightly by muscle spasm.

When the lips are everted, a midline fold of mucous membrane, known as the *frenulum*, can be seen extending from each lip to the adjacent gum. These frenula may cause problems when fitting artificial dentures. Also in the vestibule, opposite the crown of the second maxillary molar tooth, is a small eminence through which the *duct of the parotid gland* opens. These structures of the vestibule are readily visible and can usually be felt by the tongue. Many small glands are located in the mucous membrane of the lips (labial glands) and of the cheeks (buccal glands), which empty their secretions directly into the vestibule.

The lips (upper and lower) are extremely mobile folds, which form the margins of the rima oris and meet laterally at the right and left angles of the mouth, where they become continuous with the cheeks. The framework of the lip is formed by the orbicularis oris muscle, external to which is skin with its subcutaneous tissue and internal to which is the mucous membrane. The red area of the lip has an intermediate appearance between the cheek skin and the mucous membrane.

The general structure of the cheek is similar to that of the lip. The framework is formed by the buccinator muscle, strengthened by a firm fascial layer, with skin and subcutaneous tissue external to it and a mucous membrane on the internal side. On the external surface of the buccinator muscle, at the anterior border of the masseter muscle, lies the buccal fat pad, which is especially prominent in the infant.

When the tip of the tongue is turned superiorly and posteriorly, several structures come into view. In the



midline is the *frenulum of the tongue*. Immediately lateral to each side of the frenulum is a *sublingual caruncle*, at the apex of which is the opening of the submandibular duct. Running posterolaterally from the sublingual caruncle is a raised fold of mucosa caused by the underlying *sublingual gland*, with openings of several small ducts of this gland scattered along it. At each side of the undersurface of the tongue is the *fimbriated fold* and, medial to that, the *deep lingual vessels* are visible through the mucous membrane.

By direct examination of the open mouth, in addition to the structures described above, one can see the palate, the palatoglossal fold, and the palatopharyngeal fold, with the palatine tonsil between them, the teeth, and the tongue.

In an at-rest state, the upper and lower teeth are apt to be slightly separated from each other, the tongue is at least partially in contact with the palate, and the vestibule is nearly obliterated by the lips and cheeks lying against the teeth and gums.

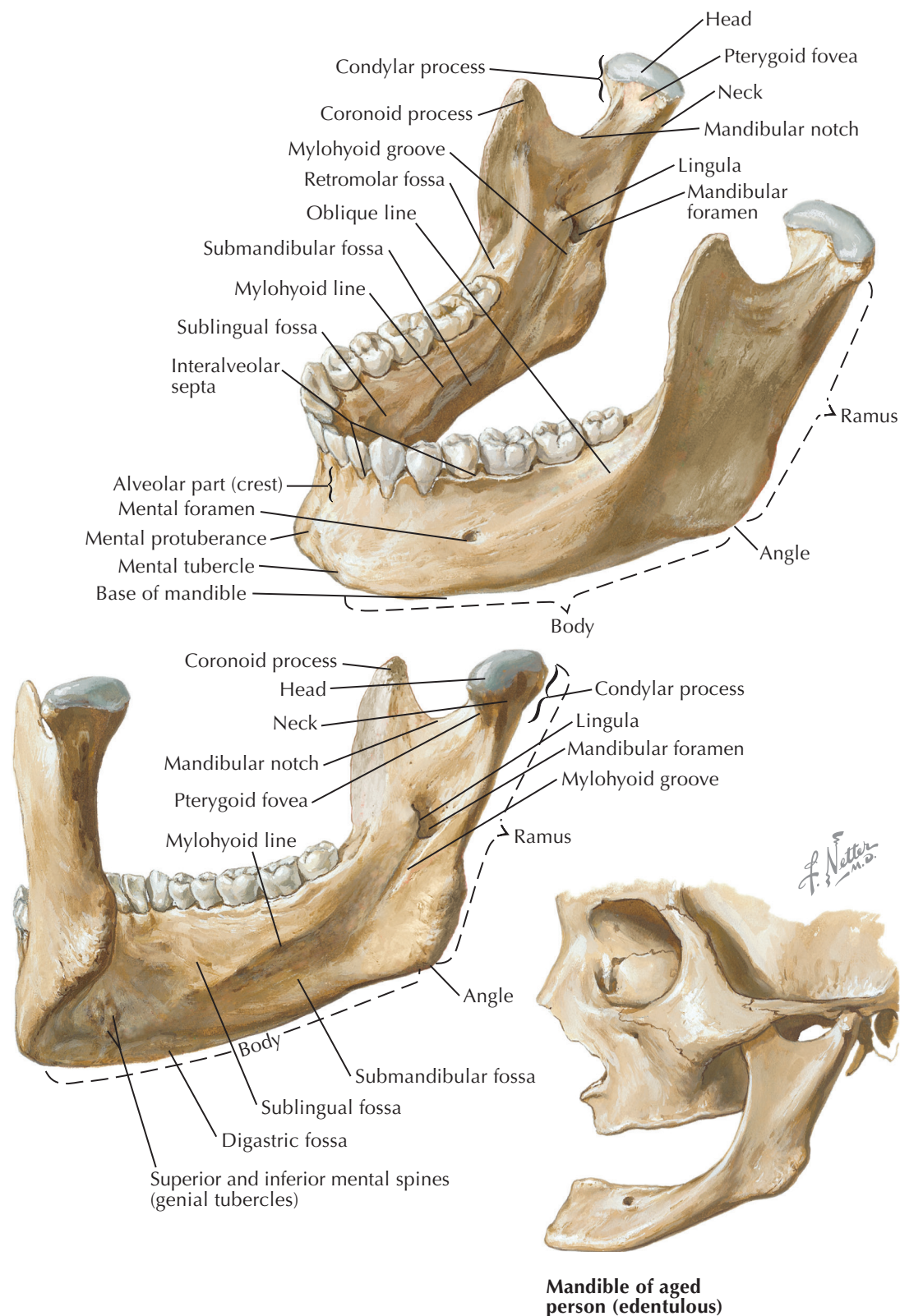
MANDIBLE

The *mandible*, or jawbone, forms the bony framework for the lower part of the oral cavity and the skeleton of the lower part of the face. It has a U-shaped body, with a broad flat ramus running superiorly from each end of the body.

The area of fusion of the right and left halves of the body of the mandible at the anterior midline is the mandibular symphysis. At the inferior anterior surface of the symphysis is a triangular elevation called the *mental protuberance*, the lower outer angles of which are the *mental tubercles*. At the inferior part of the inner surface of the symphysis is a variable elevation, the *mental spine* or spines, which may be present as a single eminence or as two eminences, one superior and the other inferior. These give origin to the geniohyoid and genioglossus muscles.

Each half of the body of the mandible has an upper and a lower part, the arch of the lower part being wider than that of the upper part. The upper part is the *alveolar process*, so called because it contains the sockets for the lower arcade of teeth. The lower part, or *body of the mandible*, has a much greater proportion of compact bone. Just lateral to the symphysis on the lower border is an oval depression or roughened area for the attachment of the anterior belly of the digastric muscle, the *digastric fossa*. On the external surface of the mandibular body, inferior to the second premolar tooth, is the *mental foramen*, by which the mental branches of the inferior alveolar nerve and vessels leave the *mandibular canal*. Also on the external surface is an ill-defined *oblique line* that runs from the mental tubercle to the anterior border of the ramus. Sometimes it may start from the lower border of the mandible inferior to the molar teeth, or there may be lines from each of these places that meet as they run posterosuperiorly. On the internal surface of the mandibular body, a ridge of bone runs obliquely from the digastric fossa to the level of the socket of the last molar tooth. This ridge gives attachment to the mylohyoid muscle and is therefore known as the *mylohyoid line*. Superior to the mylohyoid line is a shallow sublingual fossa, in which lies the sublingual gland, and inferior to the mylohyoid line is the *fossa for the submandibular gland*.

The *ramus* presents a medial and a lateral surface as well as anterior, superior, and posterior borders. The remaining border of the ramus depends on an arbitrary decision as to the dividing line between the ramus and the body; the *angle of the mandible* is the area of junction of the posterior and inferior borders of the mandible. It is usually slightly obtuse in the young adult and flares slightly laterally. In the center of the medial surface of the ramus is the *mandibular foramen*, the beginning of the mandibular canal that transmits the inferior alveolar nerve, artery, and vein. The *lingula* projects partly over the foramen from its anterior edge, and the *mylohyoid*



groove runs anteroinferiorly from it for a short distance. Projecting superiorly from the superior border of the ramus are the triangular *coronoid process* anteriorly and the *condylar process* posteriorly, with the *mandibular notch* between the two. The condylar process is subdivided into a *head* and *neck*.

The left and right halves typically fuse by the second year. The position of the mental foramen indicates changes that occur over time. At birth it is near the mandible's inferior border because the alveolar process

makes up most of the body. After full development it is about halfway between the upper and the lower borders. When an individual becomes *edentulous*, much of the alveolar process is resorbed, and the mental foramen comes to lie near or on the superior border. The angle of the mandible is more obtuse in the infant than after it has become fully developed. Again, in the edentulous state, it appears more obtuse, although this may be at least in part due to a backward tilt of the condylar process.

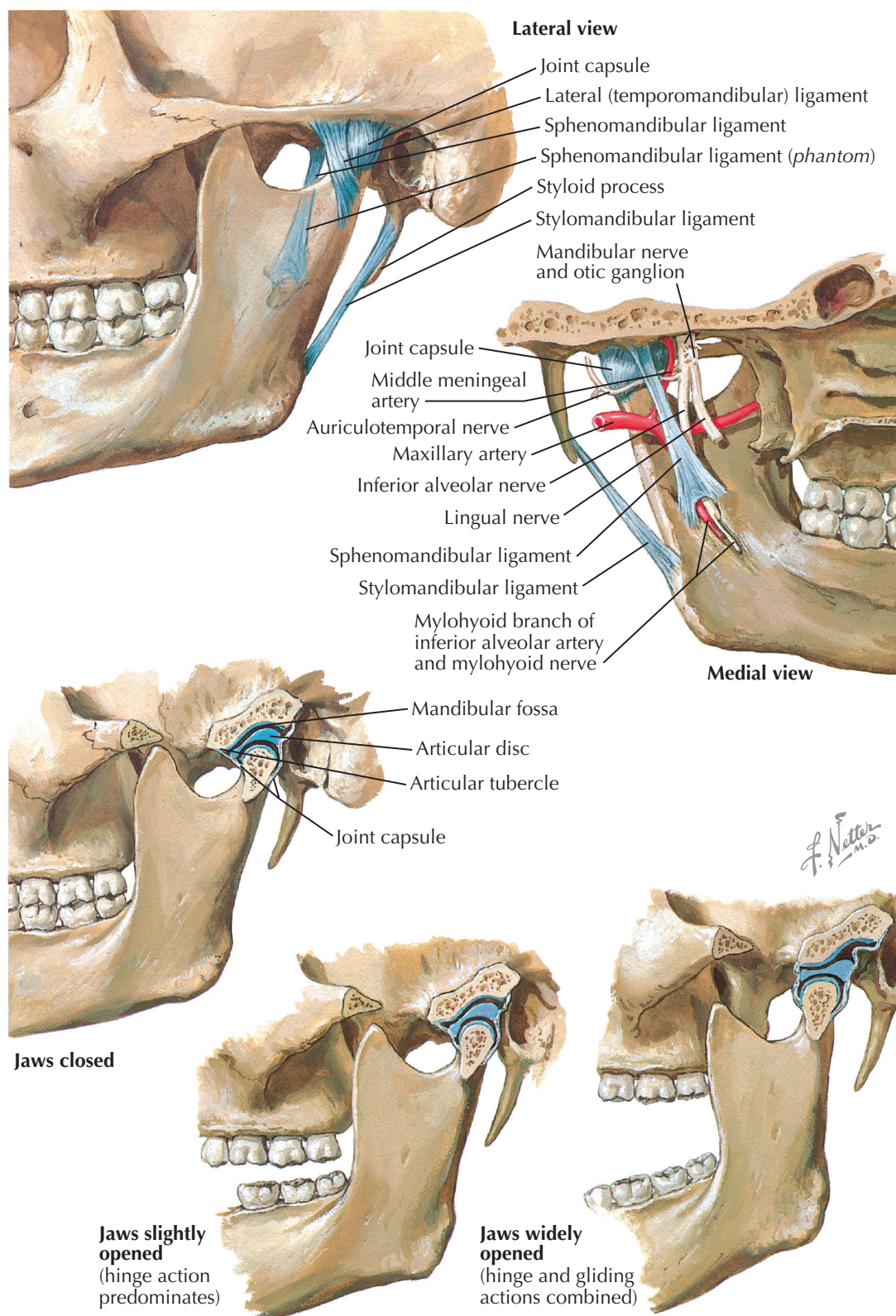
TEMPOROMANDIBULAR JOINT

The bony structures that enter into the formation of this joint are the *head of the mandibular condyle* and the *mandibular fossa* and *articular tubercle* of the temporal bone above. The head of the mandible is ellipsoidal, with the long axis directed medially and slightly posteriorly. This articular surface is markedly convex in the sagittal and coronal planes. The articular surface on the temporal bone is concave posteriorly but becomes more convex anteriorly. A fibrocartilage *articular disk* is interposed between the two articular surfaces just described. Each surface of the disk more or less conforms to the articular surface to which it is related, but the shape of the disk between individuals is quite variable. The cartilage that covers the bony articular surfaces differs from that of most joints in that it is constituted from fibrocartilage tissue rather than hyaline cartilage, although its gross appearance is similar to that of the articular cartilages of other joints.

The temporomandibular joint is a true, or synovial, joint, with two synovial spaces, one superior to the articular disk and one inferior to it. This joint can be further described as having a *hinge motion* in the lower space and a *sliding motion* in the upper space.

The temporomandibular joint is rather loosely arranged, being attached superiorly to the margin of the articular surface on the temporal bone and affixed inferiorly around the neck of the mandible. The capsular ligament is firmly attached to the entire circumference of the articular disk. Forming a pronounced thickening of the lateral aspect of the capsule is the *lateral temporomandibular ligament*, which runs inferiorly and posteriorly from the inferior border of the zygomatic process of the temporal bone to the lateral and posterior sides of the neck of the mandible. Two accessory ligaments are not blended with the capsule. The rather thin *sphenomandibular ligament* runs from the spine of the sphenoid bone to the lingula of the mandible, and the *stylomandibular ligament*, a thickened band of deep cervical fascia, runs from the styloid process to the lower part of the posterior border of the ramus of the mandible.

The temporomandibular joint receives its nerve supply from the *auriculotemporal* and *masseteric branches* of the mandibular division of the trigeminal nerve. Its arterial supply comes via branches of the maxillary and superficial temporal arteries from the external carotid artery.



The basic movements that are allowed in the temporomandibular joint are (1) gliding of the articular disk anteriorly and posteriorly on the articular surface of the temporal bone, accompanied by the head of the mandible (which moves with the disk because the disk is attached near the joint capsule's attachment to the neck of the mandible and the external pterygoid muscle is attached to both) and (2) the hinge movement that takes place between the head of the mandible and the articular disk. In opening of the mouth, both movements are

involved, with the hinge movement predominating in slight opening and the gliding movement predominating in wide opening. When chewing, one condyle remains more or less in position, while the other moves backward and forward. This is combined with slight elevation and depression of the mandible. If the mouth is opened just enough so that the upper and lower incisor teeth can clear each other, the jaw can be protracted and retracted, with the movement occurring in the upper joint.

FLOOR OF MOUTH

The term *floor of the mouth* is used differently by different authors, but in all cases it is applied to the floor of the *oral cavity proper* and does not include the *vestibule*. It is sometimes used to mean the structures that actually serve as boundaries of the cavity inferiorly. In this sense, the structures that form it would be the superior and lateral surfaces of the anterior part of the tongue and the mucous membrane that is reflected from the side of the tongue to the inner aspect of the mandible. Other authors have used the term to mean the muscular and other structures that fill the interval bounded by the mandible and the hyoid bone. This would mean primarily the mylohyoid muscle, which is then thought of as the boundary between the mouth above and the submandibular triangle of the neck below the muscle.

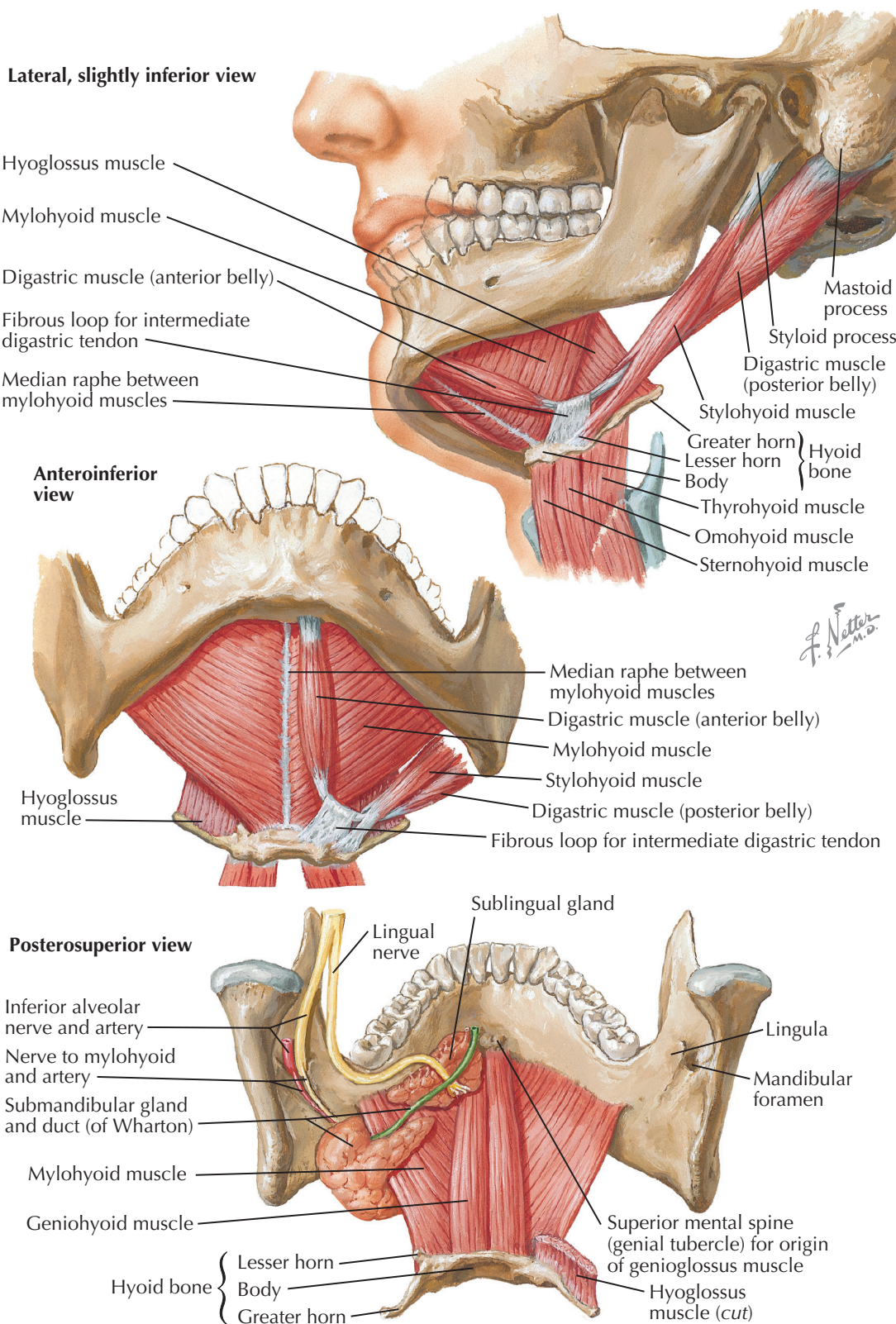
The right and left *mylohyoid muscles* form a diaphragm that is stretched between the two mylohyoid lines of the mandible and the body of the *hyoid bone*. The posterior fibers of each muscle insert on the body of the hyoid bone, and from there forward to the symphysis of the mandible the right and left muscles meet each other in a midline raphe. The mylohyoid muscle is supplied by the *mylohyoid nerve*, which is a branch of the *inferior alveolar nerve*, which itself is a branch of the mandibular division of the trigeminal nerve.

Slightly off of the midline, the *anterior belly of the digastric muscle* lies along the inferior surface of the mylohyoid muscle. Anteriorly it attaches to the digastric fossa of the mandible, and posteriorly it ends in the *intermediate tendon*, by means of which it is continuous with the *posterior belly of the digastric muscle*, which attaches to the *mastoid notch* of the temporal bone. The intermediate tendon is anchored to the hyoid bone by a *fascial loop*. The anterior belly is also supplied by the mylohyoid nerve and the posterior belly by a branch from the facial nerve.

Closely related to the posterior belly of the digastric muscle, the *stylohyoid muscle* extends from near the root of the styloid process to the greater horn of the hyoid bone. It usually attaches to the hyoid by two slips, between which the posterior belly and intermediate tendon of the digastric muscle pass. The stylohyoid is supplied by a branch of the facial nerve.

The right and left *geniohyoid muscles*, one on each side of the midline, rest on the superior surface of the mylohyoid muscle. They are attached anteriorly to the mental spines and posteriorly to the body of the hyoid bone. The geniohyoid muscle is supplied by fibers from the first cervical nerve that accompanies the hypoglossal nerve.

With the foregoing description of the related muscles in mind, the hyoid bone can be thought of as held in a muscular sling hung between the mandible and the stylohyoid region of the temporal bone, thus making



the floor of the mouth quite mobile. All of these muscles can help in the elevation of the hyoid bone and the floor of the mouth. The geniohyoid and stylohyoid muscles determine the anteroposterior position of the hyoid bone, lengthening and shortening the floor of the mouth. The infrahyoid (strap) muscles (*omohyoid*, *sternohyoid*, *sternothyroid*, and *thyrohyoid*) pull the hyoid bone and floor of the mouth inferiorly.

A usage of the term *floor of the mouth* which is less technical than the two previously given is to think of the structure as the mucous membrane that is reflected from the side of the tongue to the mandible. The attachment of the mucous membrane of this area to the mandible, where it is continuous with the gum, is along a line drawn from the posterior end of the mylohyoid line to a point just above the mental spine.

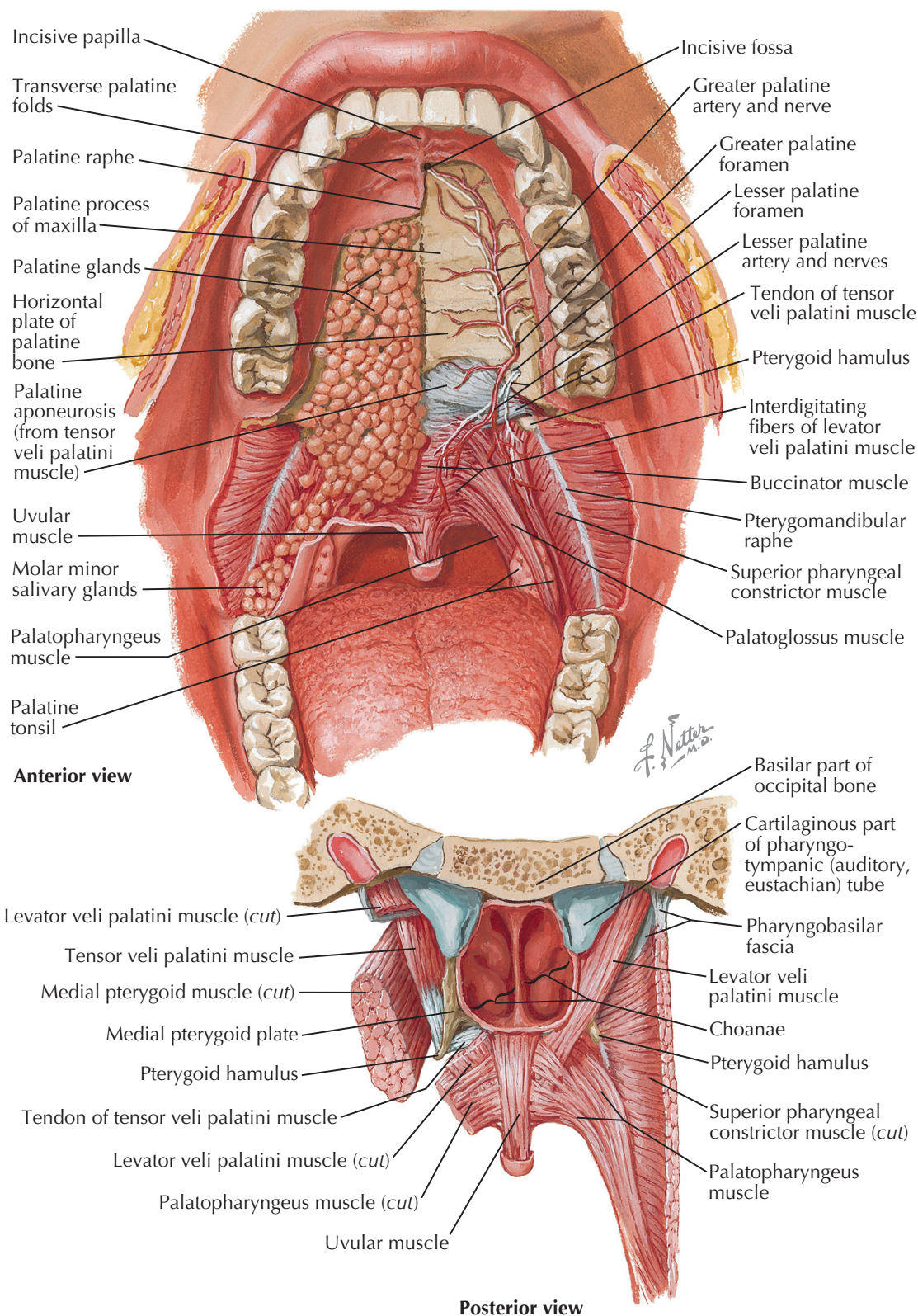
ROOF OF MOUTH

The roof of the mouth, or *palate*, forms the superior and posterosuperior boundaries of the “oral cavity proper,” which it separates from the nasal cavity and nasopharynx. The region of approximately the anterior two thirds of the palate has a bony framework and is, therefore, the *hard palate*; the posterior third is the *soft palate*. The palate is variably arched both anteroposteriorly and transversely, the transverse curve being more pronounced in the hard palate.

The bony framework of the hard palate is formed by the palatine processes of the two maxillae and the horizontal processes of the two palatine bones that meet in the midline. These bony structures also form the floor of the nasal cavity, and this common bony wall is traversed near the midline anteriorly by the *incisive canals*, which transmit blood vessels and nerves between the mucous membrane of the nose and the mucous membrane of the palate. In a posterolateral position at each side of the bony palate are the *greater and lesser palatine foramina* for the transmission of the *greater and lesser palatine vessels and nerves*. The oral surface of the bony palate is covered by mucoperiosteum (mucous membrane and periosteum fused together), which exhibits a faint midline ridge, the *palatine raphe*, at the anterior end of which is a slight elevation called the *incisive papilla*. Running laterally from the anterior part of the raphe are about six transverse ridges, the *transverse plicae*.

Anteriorly, the soft palate is continuous with the hard palate and ends posteroinferiorly in a free margin, which forms an arch, with the palatoglossal and palatopharyngeal folds on each side as its pillars. The uvula, greatly variable as to length and shape, is a projection that hangs inferiorly from the free margin of the soft palate on the midline. The framework of the soft palate is formed by a strong, thin, fibrous sheet, known as the *palatine aponeurosis*, which is partially formed by the tendons of the *tensor veli palatini* muscles. In addition to the aponeurosis, the thickness of the soft palate is made up of the *palatine muscles*, many mucous *glands* on the oral side, and a mucous membrane on both the oral and pharyngeal surfaces. The mass of glands extends forward onto the hard palate as far anteriorly as a line between the canine teeth.

The muscles of the soft palate can be briefly described as follows: (1) the *levator veli palatini* arises from the posteromedial side of the cartilaginous portion of the auditory tube and the adjacent inferior surface of the petrous portion of the temporal bone. Its anterior fibers insert in the palatine aponeurosis, and the posterior ones are continuous with those of the opposite side; (2) the *tensor veli palatini* arises from the anterolateral side of the cartilaginous portion of the auditory tube and the adjacent angular spine and the scaphoid fossa of the sphenoid bone. Its tendon passes around the



pterygoid hamulus, which acts as a pulley, and then spreads out into the palatine aponeurosis; (3) the *uvular muscle* arises from the posterior nasal spine and palatine aponeurosis, and unites with its counterpart on the other side to end in the mucous membrane of the uvula; (4) the *palatoglossus muscle* runs from the soft palate to the side of the tongue; and (5) the *palatopharyngeus muscle* runs from the soft palate inferiorly into the pharyngeal wall. These muscles are supplied by vagus nerve fibers, probably from the cranial part of the spinal

accessory nerve, except for the tensor veli palatini, which is supplied by the mandibular branch of the trigeminal nerve.

By means of the actions of the described muscles, the soft palate can be positioned as necessary for swallowing, breathing, and phonation. It can be brought into contact with the dorsum of the tongue and it can be brought up against the wall of the pharynx, which is important in closing off the nasopharynx from the oropharynx during swallowing.

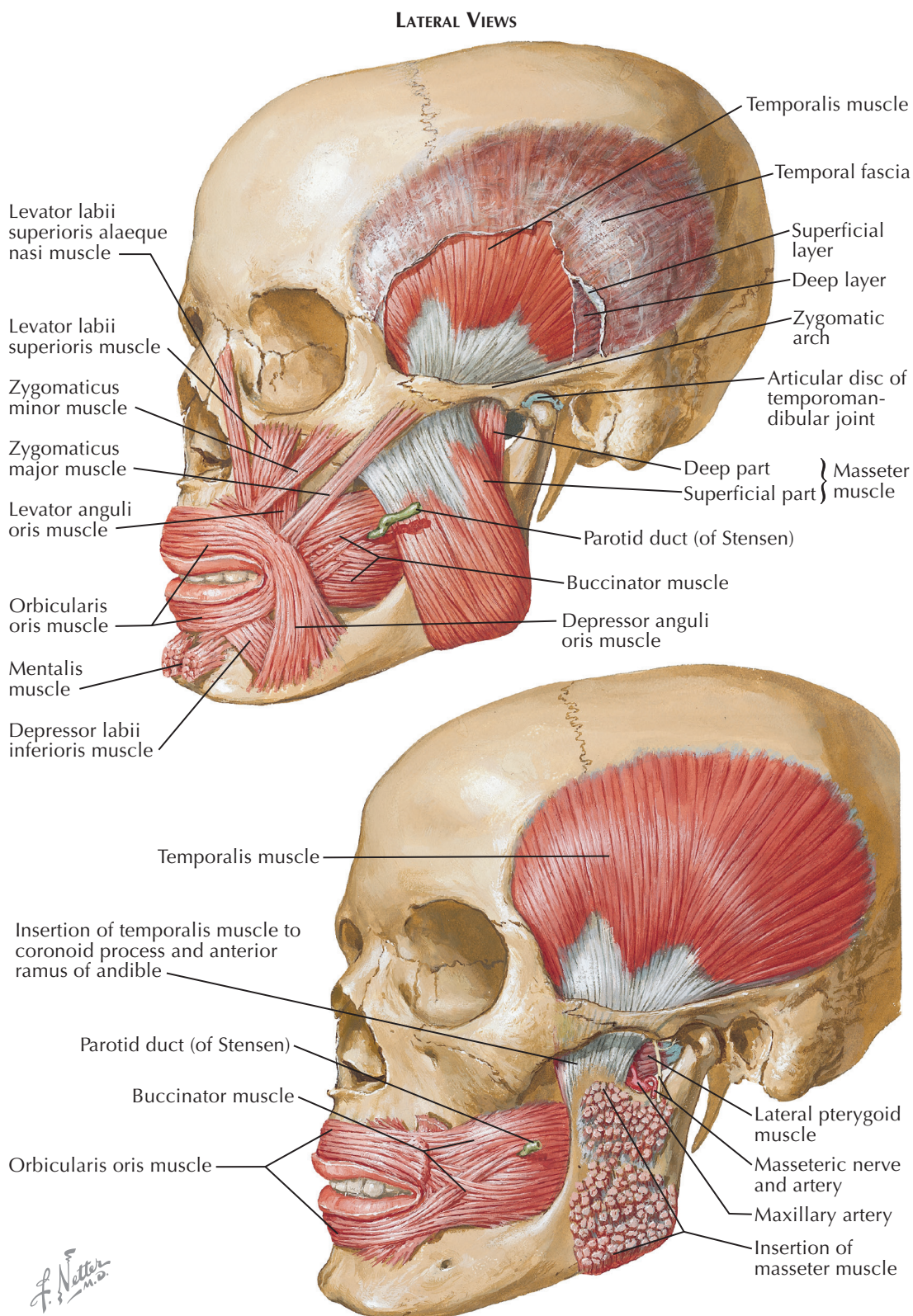
MUSCLES INVOLVED IN MASTICATION

Chewing, or mastication, is one of the important functions carried on in the mouth, and a number of muscles are involved either directly or indirectly in this activity. However, the four muscles that are primarily responsible for the forceful chewing movements of the mandible are classified by most authors as the "muscles of mastication." These are the masseter, temporalis, lateral pterygoid, and medial pterygoid muscles.

The *masseter muscle* is a thick, quadrangular muscle that is readily palpable on the side of the jaw. It is described as having a superficial and a deep part, which can be rather easily separated on the posterior aspect of the muscle but are blended together anteriorly. The *superficial part* arises from the inferior border of the anterior two thirds of the zygomatic arch (zygomatic process of maxilla, zygomatic bone, and zygomatic process of temporal bone) and runs medially and a little posteriorly to insert on the lateral surface of the lower part of the ramus of the mandible. The area of insertion continues to the inferior border of the mandible. The *deep portion* of the masseter muscle arises from the inner surface of the whole length of the zygomatic arch and runs almost vertically inferiorly to insert on the lateral surface of the coronoid process and upper part of the ramus of the mandible. The deepest fibers frequently blend with the adjacent portion of the temporalis muscle. The masseter muscle is supplied by a masseteric branch from the mandibular division of the trigeminal nerve, which reaches the deep surface of the muscle by passing through the mandibular notch.

The *temporalis muscle*, spread out broadly on the lateral side of the skull, is a thin sheet, except where its fibers converge toward the tendon of insertion. It arises from the whole temporal fossa (the extensive area between the inferior temporal line and the infratemporal crest) and from the inner surface of the *temporal fascia* that covers the muscle. The temporalis muscle inserts by means of a thick tendon that passes medial to the zygomatic arch and attaches to the apex and deep surface of the coronoid process of the mandible and the anterior border of the ramus almost as far as the last molar tooth, with some of the fibers frequently becoming continuous with the buccinator muscle. Two or three deep temporal branches of the mandibular nerve enter the deep surface of the temporalis muscle.

The *lateral pterygoid muscle* is somewhat conical in shape and runs horizontally in the infratemporal fossa. It arises as the fusion of superior and inferior heads.



The superior head attaches to the infratemporal surface of the greater wing of the sphenoid bone, and the inferior head attaches to the lateral surface of the lateral pterygoid plate. The two heads join and form a tendon of insertion that ends on the front of the condylar neck of the mandible and on the anterior aspect of the capsule and articular disk of the temporomandibular joint. A lateral pterygoid nerve from the mandibular branch of the trigeminal enters the deep surface of this muscle.

The *medial pterygoid muscle*, located medial to the ramus of the mandible, is thick and quadrangular. Its main origin is from the medial surface of the lateral pterygoid plate and from the pyramidal process of the palatine bone between the two pterygoid plates. A small slip of muscle originates from the tuberosity of the maxilla and the adjacent surface of the pyramidal process of the palatine bone. The medial pterygoid muscle inserts on the medial surface of the ramus of the mandible between the mylohyoid groove and the angle.

LATERAL AND POSTERIOR VIEWS

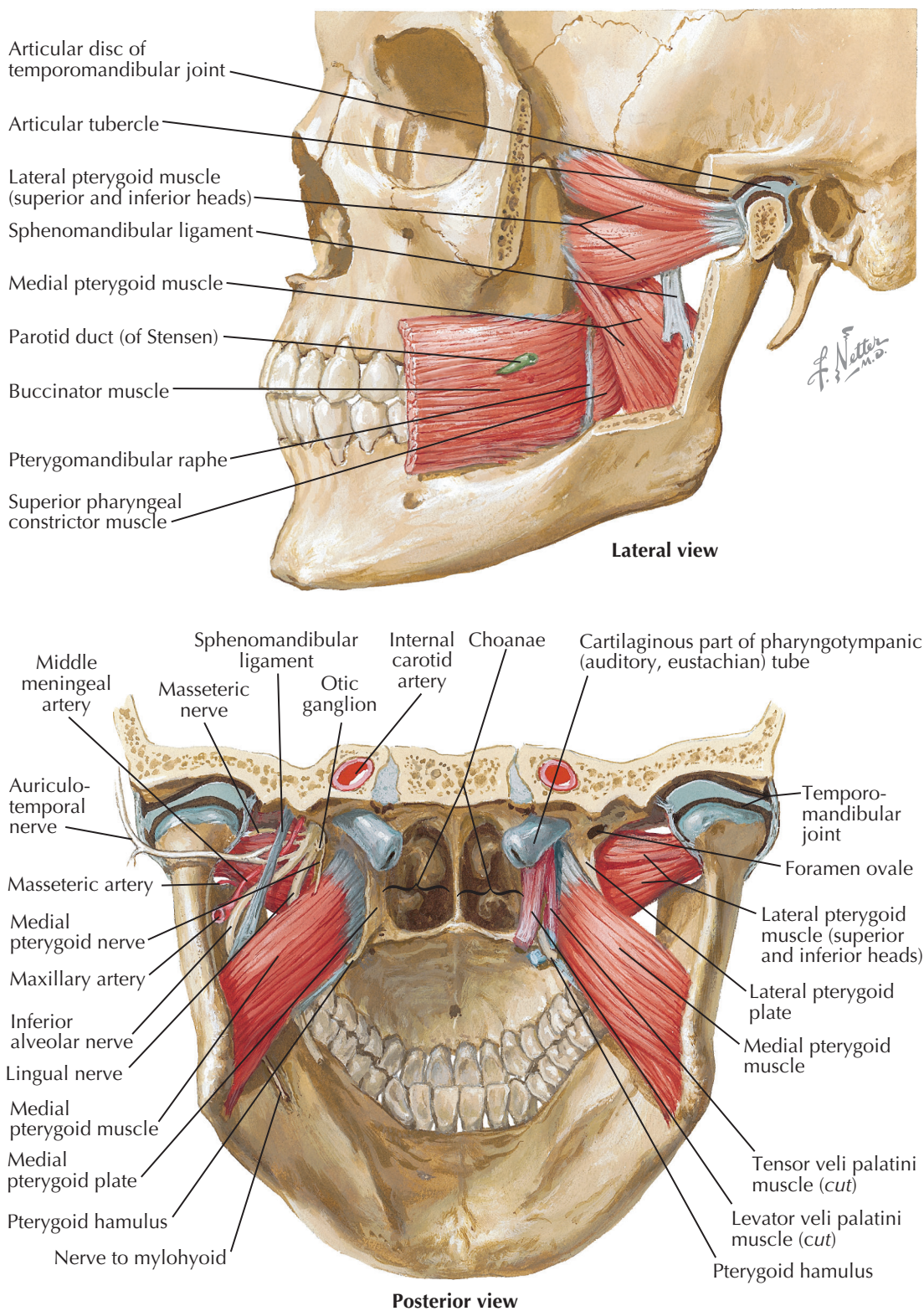
MUSCLES INVOLVED IN MASTICATION (Continued)

The medial pterygoid nerve from the mandibular runs along the medial side of the muscle to enter it.

The muscles of mastication all pass across the temporomandibular joint, and they are the major muscles producing the movements allowed at this joint. Elevation of the mandible is brought about by the masseter, temporalis, and medial pterygoid. They are able to bring the lower teeth powerfully up against the upper teeth. They also are acting against gravity in most positions of the head in keeping the mouth closed. If they are relaxed, the weight of the jaw can gap the mouth to a small degree. The muscle of mastication that actively opens the mouth is the lateral pterygoid. It does this by pulling the articular disk and condyle of the mandible anteriorly. Other muscles that help in opening the mouth against resistance are the suprahyoid, infrahyoid, and platysma muscles. Protrusion of the jaw is brought about primarily by bilateral contraction of the lateral pterygoid, because in this movement, also, the articular disk and condyle of the mandible are brought anteriorly. The superficial portion of the masseter and the medial pterygoid can give some minor aid in protrusion. Retraction of the mandible is accomplished mostly by the posterior part of the temporalis muscle, some of the fibers of which run nearly horizontally. The digastric and geniohyoid muscles can contribute to retraction when the hyoid bone is anchored.

All the muscles of mastication are employed in the act of chewing, because it involves the four movements of the mandible described above (i.e., elevation, depression, protrusion, and retraction) and at least one of the muscles of mastication is involved in each of these movements. For the most part, chewing is done either on one side or the other, and the condyle of the side on which the chewing is being done remains more or less in position while the condyle of the other side moves back and forth, as in protrusion and retraction. This is combined in proper sequence with slight elevation and depression to bring about the grinding action on the food.

In order that grinding can be carried on efficiently, the food must be kept between the teeth by the tongue on one side and the cheek and lips on the other side. Naturally, the muscular framework of the cheek and lips is important in accomplishing this. The framework of the cheek is formed by the *buccinator muscle*, which takes



its origin from the outer surfaces of the maxilla and mandible in the region of the molar teeth and between the posterior ends of these lines of attachment from the pterygomandibular raphe, by means of which it is continuous with the superior constrictor of the pharynx. From this U-shaped origin, the horizontal fibers of the muscle run anteriorly, apparently to continue into the *orbicularis oris muscle*, with the superiormost and inferiormost fibers going into the upper and lower lips, respectively, and the intermediate fibers crossing near

the corner of the mouth, so that the superior fibers of this intermediate group go into the lower lip and the inferior fibers of the intermediate group go into the upper lip. The buccinator muscle is supplied by the facial nerve. The framework of the lips is formed by the *orbicularis oris muscle*. In addition to the fibers that appear to be the forward prolongations of the buccinator muscle, fibers come into the *orbicularis oris muscle* from all of the muscles that insert in the vicinity. The *orbicularis oris muscle* is also supplied by the facial nerve.

TONGUE

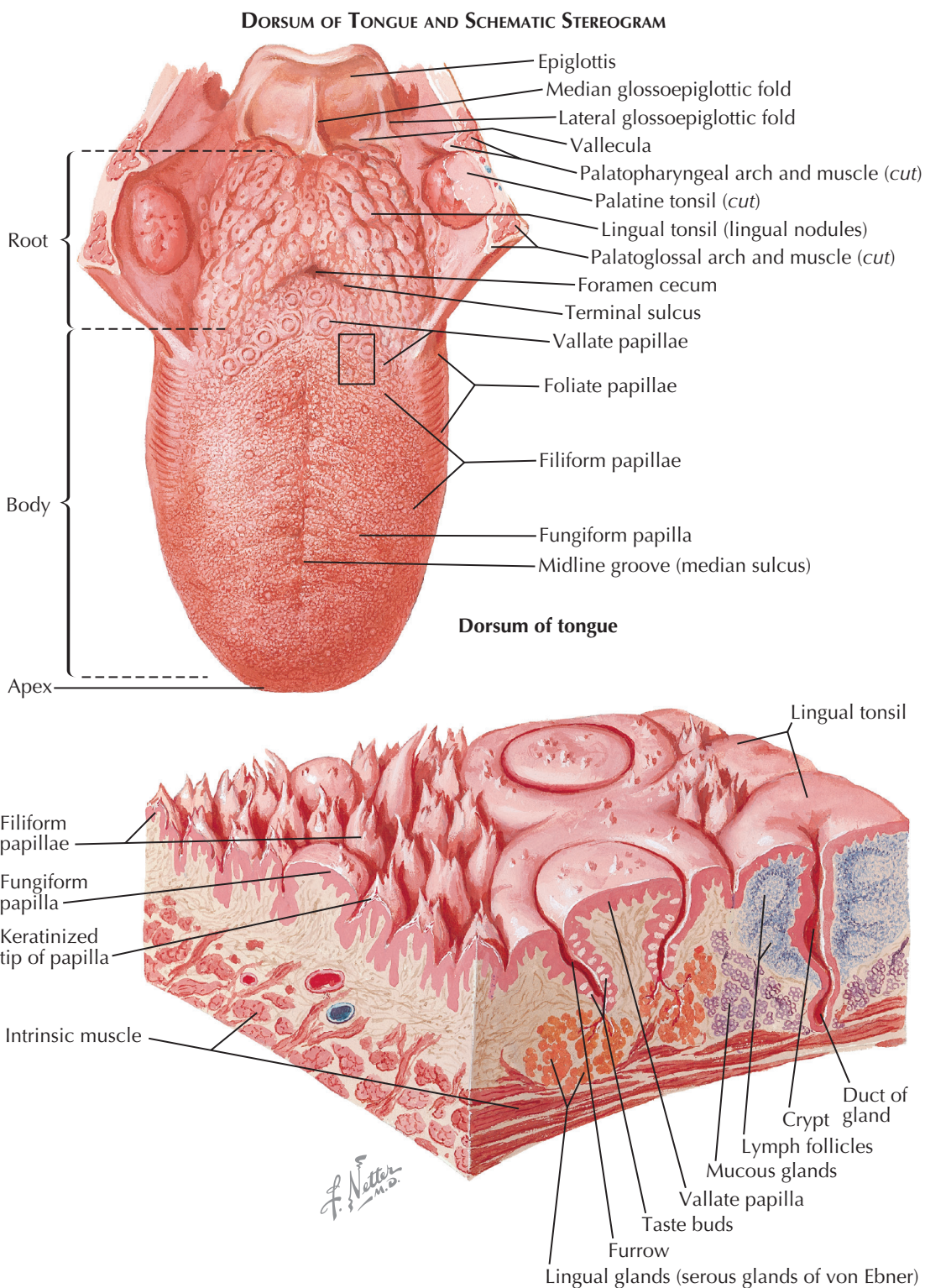
The tongue is an extremely mobile mass of striated muscle, covered by mucous membrane. Arising from the floor of the mouth, the tongue practically fills the oral cavity when all its parts are at rest and the individual is in an upright position. The shape of the tongue may change extensively and rapidly during the various activities it has to perform.

The areas of the tongue covered by the mucous membrane are the *apex*, the *dorsum*, the right and left margins, and the inferior surface. These are obvious topographic designations, except for the dorsum, which needs further description. The dorsal aspect of the tongue extends from the apex to the reflection of the mucous membrane to the anterior surface of the *epiglottis* at the *vallecula*, forming an arch that, in its anterior or palatine two thirds, is directed superiorly, whereas its posterior or pharyngeal one third is directed posteriorly. Several divisions of the tongue have been proposed. Sometimes the *terminal sulcus* has been said to separate the *body* and the *root* of the tongue, but in other instances the portion called the root has been limited to the posterior and inferior attachment of the tongue or has even been restricted to mean only the region of attachment through which muscles and other structures enter and leave the tongue. From the practical point of view, it is rather irrelevant where one permits the root to start and the body to end, or vice versa, but it is important to realize that the posterior third of the tongue and its epiglottic region are not visible by simple inspection even if the tongue is protruded unless the examiner uses a mirror or presses the tongue down with the aid of a spatula.

At the posterior end of the body is a small blind pit, known as the *foramen cecum*, the remnant of the thyroglossal duct, from which the thyroid gland developed during the fetal stage. Angling anterolaterally toward each side from the foramen cecum is the terminal sulcus, which is usually referred to as the dividing line between the anterior and posterior parts of the tongue. However, the real dividing line may run just anterior to the vallate papillae. A *median sulcus* is not always very distinct but is related to the interior, *lingual septum*.

The mucous membrane covering the apex and body of the tongue is moist and pink and is thickly studded with various *papillae*. The majority of the papillae are of the *filiform* type, in which the epithelium ends in tapered, rough points to provide friction for the handling of food. Scattered about the field of filiform papillae are the larger, rounded *fungiform* papillae. In front of the sulcus terminalis runs a V-shaped row of 8 to 12 (circum) *vallate* papillae, which rise far more prominently over the surface of the mucous membrane than do the two other types of papillae. The whole mucosa of the anterior two thirds of the tongue is firmly adherent to the underlying tissue.

The mucous membrane of the posterior one third of the tongue (the pharyngeal part), though smooth and glistening, has an uneven or nodular surface owing to the presence of a varying number (35 to 100) of rounded elevations with a crypt in the center. These nodules consist of lymphoid tissue lying deep to the epithelium.



Schematic stereogram: area indicated above

The lymphoid nodules are grouped around the epithelium-lined crypt or pit and, taken collectively, are called the *lingual tonsil*.

On both margins of the tongue, the mucous membrane is thinner and, for the most part, devoid of papillae, though a variable number of vertical folds may be found on the posterior part of each margin. They are called *foliate papillae*, and represent rudimentary structures similar to the well-developed foliate papillae seen in rodents.

The mucous membrane of the inferior surface of the tongue is thin, smooth, devoid of papillae, and more loosely attached to the underlying tissue. It exhibits the midline frenulum and some rather rudimentary fimbriated folds that run posterolaterally from the tip of the tongue. The frenulum is a duplication of the mucous membrane and connects the inferior lingual surface with the floor of the mouth. The deep lingual veins usually shine through the mucosa between the frenulum and the fimbriated folds on each side.

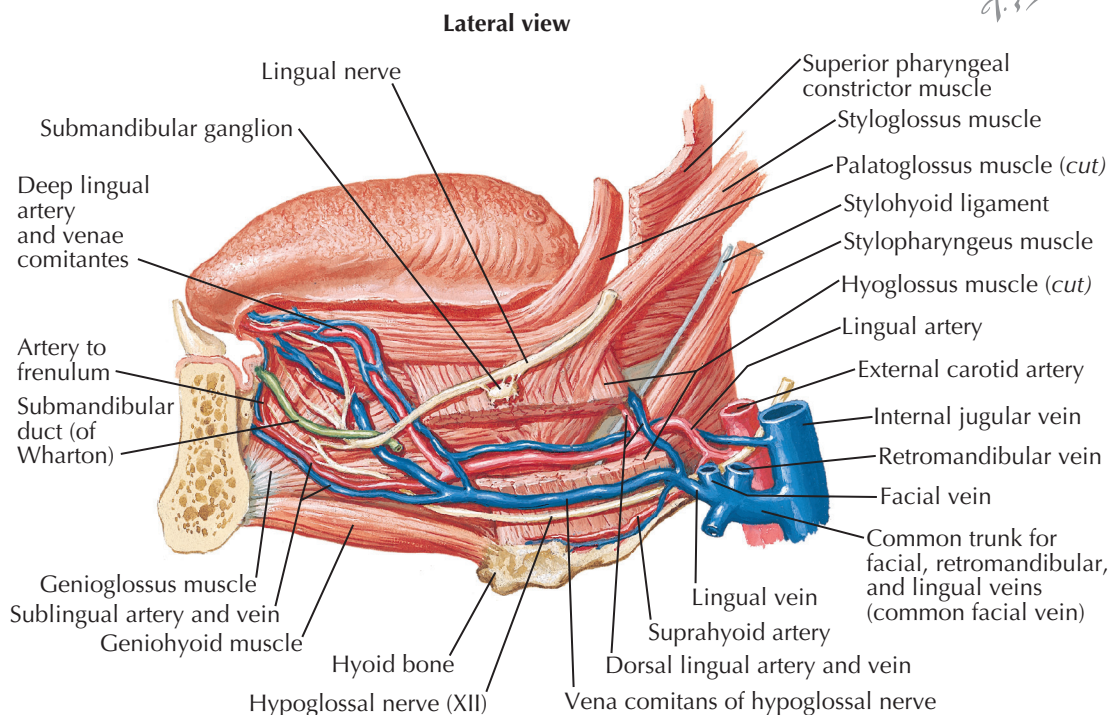
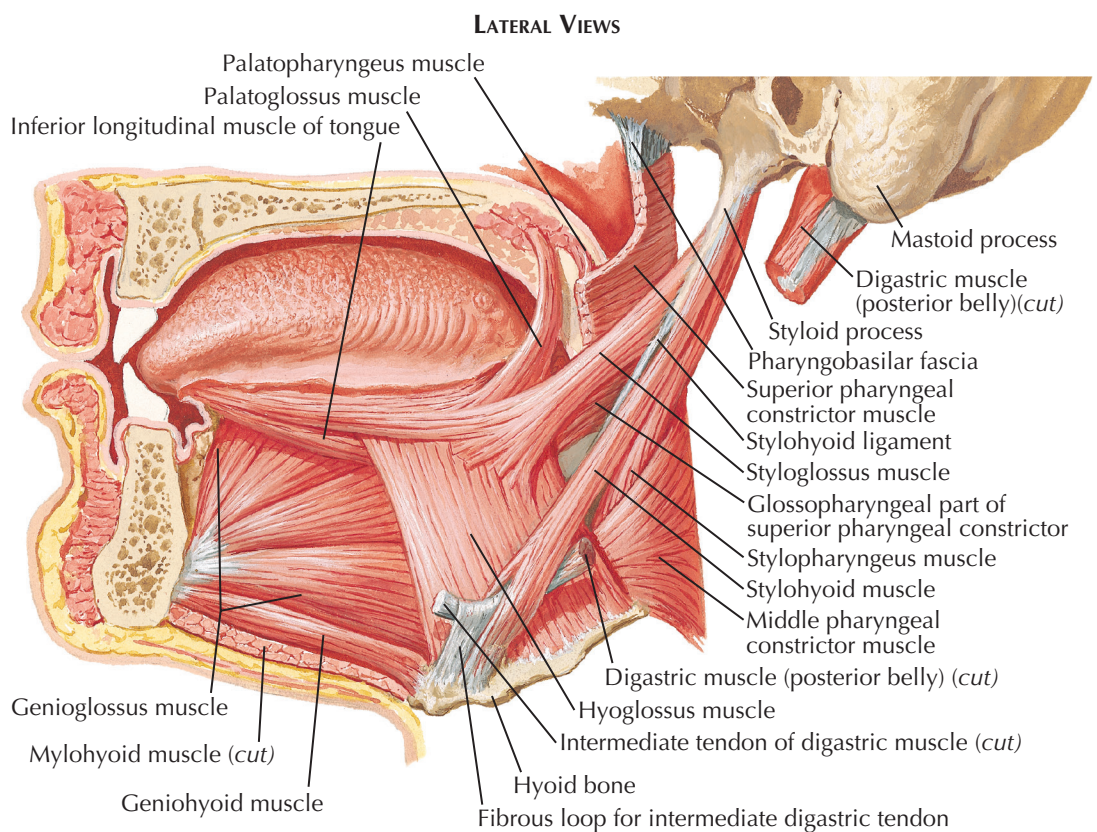
TONGUE (Continued)

Many small glands are scattered beneath the mucous membrane and partly embedded in the muscle. *Mucous glands* are located in the posterior third of the dorsum, with their ducts opening on the surface and into the pits of the lingual tonsil. In the region of the vallate papillae, the purely serous *lingual glands of von Ebner* send numerous ducts (from 4 to 38) into the furrows, or moat, surrounding each of these papillae. Glands of a mixed type, the lingual glands of Blandin and Nuhn, are found to each side of the midline inferior and posterior to the apex of the tongue.

The receptor organs for the sense of taste, the *taste buds*, are pale oval bodies (about 70 μ in their long axis), seen microscopically in the epithelium of the tongue and to a much lesser extent in the epithelium of the soft palate, pharynx, and epiglottis. The taste buds are most prevalent in the epithelial lining of the furrows surrounding the vallate papillae. A few taste buds are present on the fungiform papillae and also scattered on the foliate papillae. A taste bud reaches from the basement membrane to the epithelial surface, where a *pore* is situated, into which the microvilli (taste hairs) of the neuroepithelial *taste (gustatory) cells* extend. From 4 to 20 taste cells are intermingled with the more numerous supporting *sustentacular cells* of the taste buds.

The majority of the tongue is made up of skeletal (striated) muscles, which are composed of muscular bundles, interlaced in many directions. An incomplete *lingual septum* divides the tongue into symmetric halves. One group of muscles, the extrinsic ones, originates outside of the tongue, whereas the intrinsic group of lingual muscles originates and inserts entirely within other muscles of the tongue. The *genioglossus muscle* arises from the superior mental spine of the mandible and fans out along the entire length of the dorsum of the tongue, with the lowest fibers having some attachment to the hyoid bone. Lateral to this muscle is the *hyoglossus muscle*, which arises from the body of the hyoid bone as well as the entire length of the greater and lesser horns from which it runs vertically upward. The *styloglossus muscle* arises from near the tip of the styloid process and an adjacent part of the stylomandibular ligament. It runs as a band inferiorly and anteriorly onto the lateral aspect of the tongue. The *palatoglossus muscle* descends from the soft palate, forming the framework of the palatoglossal fold. The intrinsic lingual muscles are named according to the three spatial dimensions in which their fascicles run. Of the two longitudinal muscles, the *superior longitudinal band* extends from anterior to posterior just deep to the mucous membrane of the dorsum. The *inferior longitudinal band* spreads between the genioglossus and hyoglossus muscles on the undersurface of the tongue.

The contraction of both longitudinal muscles shortens the tongue. The transverse lingual muscle, which is covered by the superior longitudinal muscle, furnishes nearly all of the transversely running fibers and is intermingled with fascicles of the extrinsic muscle group.



The vertical lingual muscle is made up of all the vertical fibers, except those supplied by extrinsic muscles, with which it forms a closely woven network. By the combined actions of all these muscles, the shape of the tongue can be extensively altered: lengthened, shortened, broadened, narrowed, curved in various directions, protruded, and drawn back into the mouth.

The innervation of the tongue involves the following nerves: (1) motor from the hypoglossal nerve except for

the palatoglossus muscle, which is innervated by the vagus nerve; (2) general sensory to the anterior two thirds via the lingual nerve, which is accompanied by the chorda tympani, a branch of the facial nerve, which is special sensory (taste) to the same area; and (3) glossopharyngeal nerve, which is general and special sensory to the posterior one third of the tongue. The vagus nerve is general and special sensory to the epiglottic region.

TEETH

The teeth are specialized structures that bite or tear off the pieces of solid food that enter the oral cavity and chop and grind this food as it is being mixed with saliva in preparation for swallowing. The muscles of mastication are responsible for the movements of the lower teeth in relation to the upper teeth, and the tongue and cheeks are responsible for positioning food between the teeth as necessary.

Humans develop two sets of teeth, a deciduous set (milk teeth), which begin to come in at about the age of 6 months, and a so-called permanent set, which gradually begin to replace the deciduous set at about the age of 6 years.

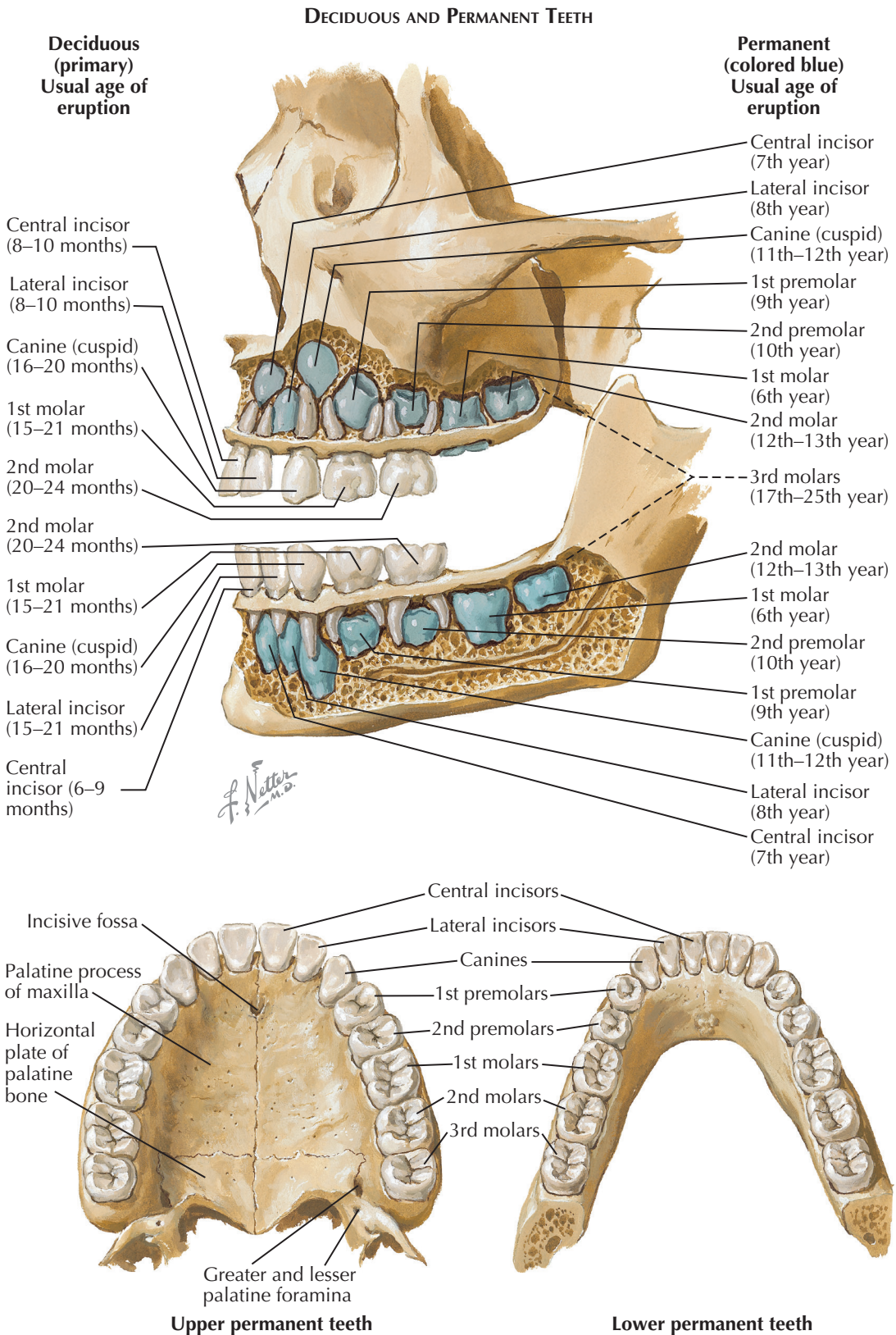
The *deciduous teeth* number 20 in all, 5 on each side of the upper and lower jaws. Starting at the midline of each jaw and progressing laterally and posteriorly to each side, the deciduous teeth are named in order: *central (medial) incisor*; *lateral incisor*; *canine (cuspid)*; *first molar*; and *second molar*. The four teeth of the same name are differentiated by designating which jaw and which side of the jaw, as right or left upper (maxillary) or lower (mandibular) central incisor. The deciduous teeth are smaller than the permanent teeth that take their position.

The *permanent teeth*, once all have come in, number 32, 8 on each side of the upper and lower jaws. Starting at the midline of each jaw and progressing laterally and posteriorly to each side, the permanent teeth are named in order: *central (medial) incisor*; *lateral incisor*; *canine (cuspid)*; *first premolar* (bicuspid), *second premolar* (bicuspid), *first molar*; *second molar*; and *third molar* (wisdom tooth). The incisors, and to some extent the canines, are adapted for biting the food, whereas the molars, and to some extent the premolars, are adapted for grinding and pounding food.

Normally, the upper dental arch is wider than the lower dental arch, and the upper incisors and canines overlap the lower incisors and canines. When the jaws are closed (in occlusion), the teeth of the two jaws come into contact in such a way that their chewing surfaces fit each other, which means that the teeth of one jaw are not exactly opposite the corresponding teeth of the other jaw. In spite of this, because the lower molars, especially the third molars, are longer anteroposteriorly, the dental arches end at approximately the same place posteriorly. Teeth are described as having a labial (buccal) surface, a lingual surface, and a contact surface.

Ordinarily, none of the teeth have erupted before birth, but all of the deciduous teeth usually come in between the sixth month and the end of the second year. The time of eruption varies considerably as does any timetable of development. The possible range of the time at which each deciduous tooth may erupt is indicated in the parentheses below the name of each tooth in the accompanying illustration.

From the end of the second year until the sixth year, no visible change in the teeth takes place. At about the sixth year, the first permanent molar comes in posterior to the second deciduous molar, and it is important that



this be recognized as a permanent tooth and given the care that a permanent tooth merits. Starting in the seventh year, gradual replacement of the deciduous teeth by the permanent teeth takes place, which is usually completed by the twelfth year. The second molar, as a rule, emerges about this time, and the third molar, if it erupts at all, several years later. The approximate time at which each permanent tooth may erupt is specified in the accompanying illustration below the name of the tooth. The developing permanent teeth are

present within the jaw long before they erupt. Obviously, during the eruption of the teeth, growth changes must occur in the jaws.

The *crown* of a tooth is the portion of the tooth projecting beyond the gum. It differs in shape in different types of teeth, the difference being related to the functional adaptation of the tooth. The crown of an incisor is chisel shaped, that of a canine is large and more conical, and the crowns of the premolars and molars are flattened and broad, with tubercles.

TEETH (Continued)

The *neck* of a tooth is the short, constricted portion that connects the crown and the root.

The *root* of a tooth is the portion embedded in the alveolar process of the jaw. It is long, tapering, and fitted to its socket. The root of an incisor is usually single, the canine has a single long root, and that of a premolar is usually single, flattened anteroposteriorly, and grooved, with some tendency to division. Each molar has two roots, an anterior root and a posterior root, which are apt to be wide, flattened anteroposteriorly, grooved, and perhaps partially divided. At the tip (or tips) of each root is a minute opening called the *apical foramen*, which allows passage for blood vessels and nerves to the root.

The interior of a tooth contains a space called the cavity of the tooth (pulp cavity), which is filled in the natural state by loose connective tissue, capillaries, nerves, and lymphatics, collectively called the *pulp*, on the outer surface of which is a layer of cells called *odontoblasts*. The cavity extends into each root as the tapering *root canal*, which ends at the apical foramen.

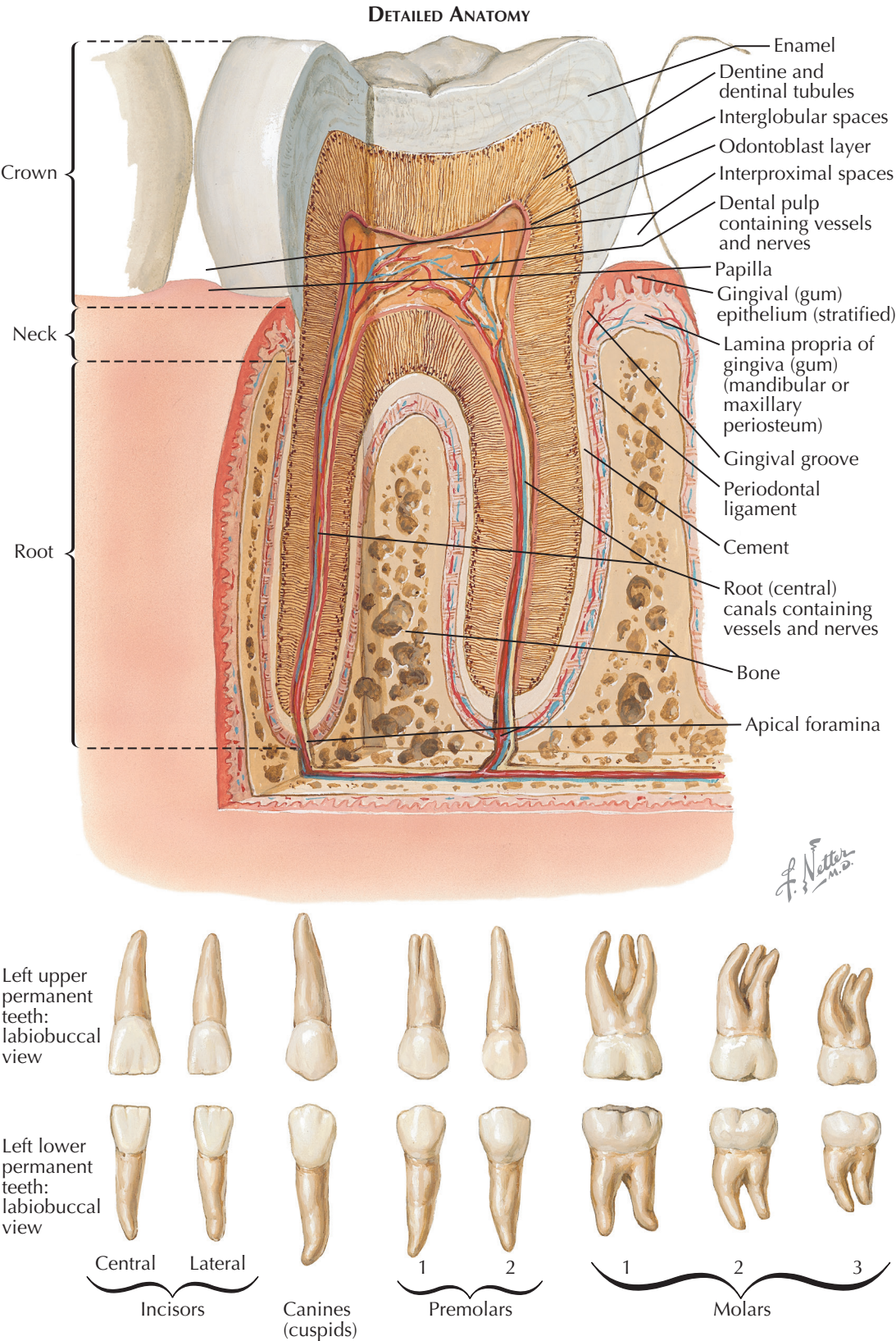
Surrounding the cavity is the *dentin*, which constitutes the mass of the tooth and is a hard, highly calcified (only 28% organic matter), homogeneous material. It is traversed by *dental tubules* (dental canaliculi) extending from the cavity to the outer margin of the dentin. The dental tubules are occupied by processes of the *odontoblasts*, which create the dentin.

Forming a cap over the dentin of the crown is the dense, white, and glistening *enamel*, the hardest (only about 3% organic material) and most resistant material in the body. It is made up of solid, hexagonal prisms (enamel prisms), which are oriented essentially perpendicular to the related surface of the crown. It is created within the gums by cells called *ameloblasts*.

Cementum, modified bone having lamellae, canaliculi, and lacunae, covers the dentin of the roots. It is very thin at its beginning at the neck and increases in thickness toward the root's apex.

The root of the tooth is united to the wall of the socket by an important layer of vascular fibrous connective tissue, the alveolar periosteum or *periodontal ligament*. This layer is continuous with the lamina propria of the gum at the alveolar process margin (near the neck of the tooth).

The covering of the internal and external surfaces of the alveolar processes of the maxilla and mandible, the *gums* or *gingivae*, is made up of *stratified squamous epithelium*, resting on a thick, strong *lamina propria*, which is firmly attached to the underlying bone. This, being a fusion of mucous membrane and periosteum, could be called *mucoperiosteum*. The gum forms a free fold,



which surrounds the base of the crown of the tooth for a short distance like a collar.

The arteries and nerves that supply the teeth are branches of the superior and inferior alveolar arteries and nerves. These travel partly to the pulp cavity and partly to the surrounding periodontal ligament. Branches to the pulp cavity travel by way of the apical foramen and root canal. The vessels form a rich capillary plexus under the odontoblast layer.

The enamel of the tooth originates from the oral ectoderm, which differentiates into ameloblasts, and the rest of the tooth comes from the mesenchymal tissue of the maxillary and mandibular arches. The ameloblasts and odontoblasts create a bell-shaped structure as they lay down enamel and dentin to create the tooth within the mesenchyme. The mesenchyme remains in the dental pulp, allowing the alveolar vessels and nerves to reach the developing tissues.

SALIVARY GLANDS

Numerous glands secrete the watery, somewhat viscous fluid known as *saliva* into the oral cavity. Small salivary glands are widely scattered under the lining of the oral cavity and are named, according to their location, *labial*, *buccal*, *palatine*, and *lingual glands*. The three chief, large, paired salivary glands are the parotid, submandibular, and sublingual.

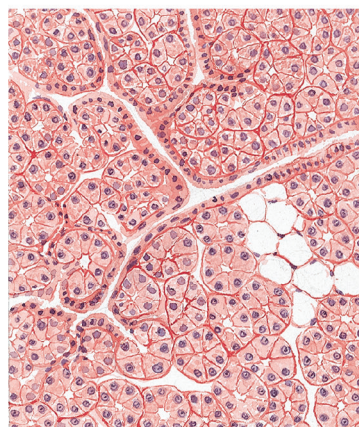
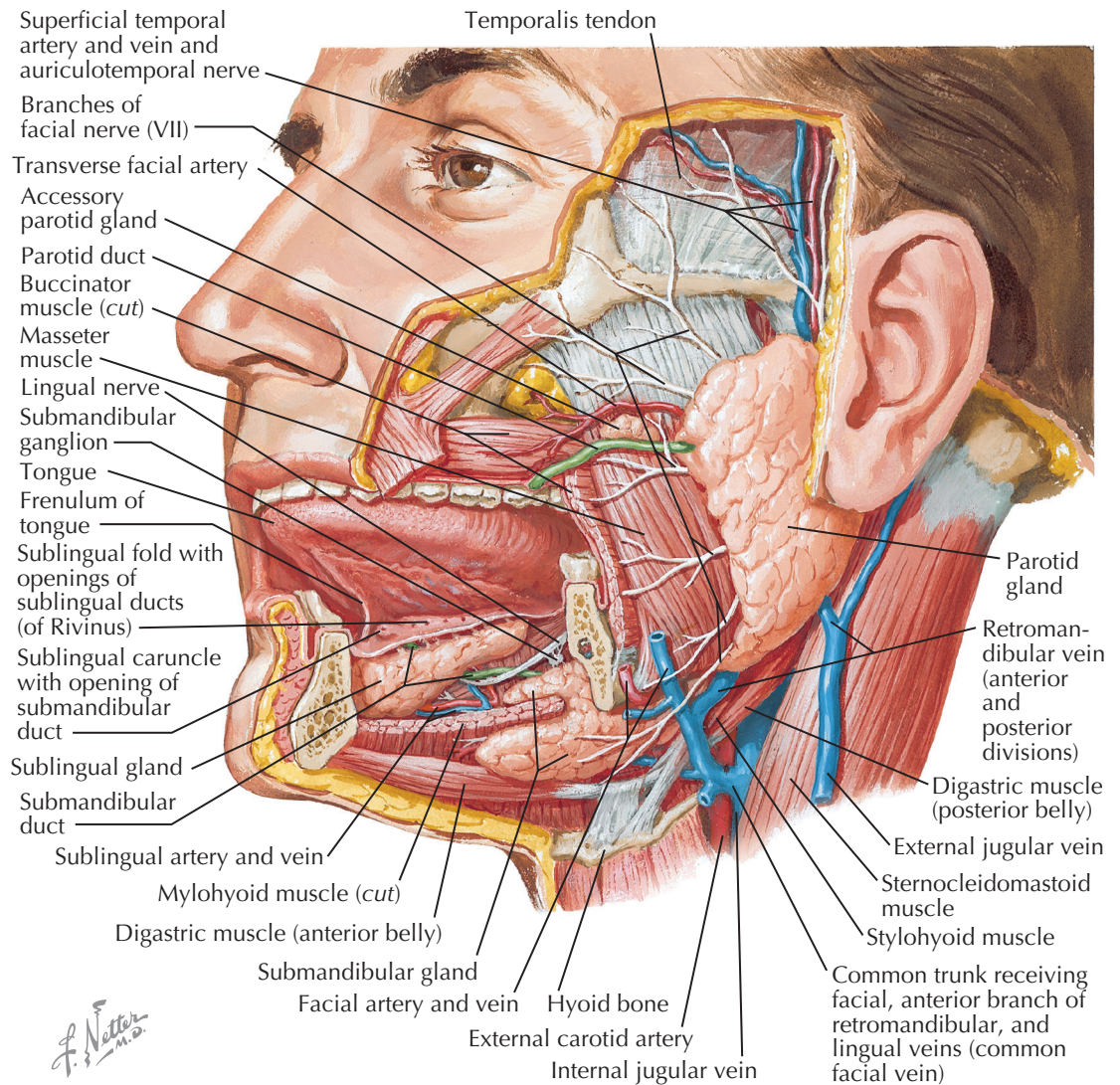
The *parotid gland*, the largest of the salivary glands, is roughly shaped as a three-sided wedge, which is fitted in anterior and inferior to the external ear. The triangular superficial surface of the wedge is practically subcutaneous, with one side of the triangle almost as high as the zygomatic arch and the opposing angle at the level of the angle of the mandible. The anteromedial side of the wedge abuts against and overlaps the ramus of the mandible and the related masseter and medial pterygoid muscles. The posteromedial side of the wedge turns toward the external auditory canal, mastoid process, sternocleidomastoid, and digastric (posterior belly) muscles. The *parotid (Stensen) duct* leaves the anterior border of the gland and passes superficial to the *masseter muscle*, at the anterior border of which it turns medially to pierce the *buccinator muscle* and then the mucous membrane of the cheek near the second maxillary molar.

The *submandibular gland* lies in the submandibular triangle but overlaps all three sides of the triangle, extending superficial to the anterior and posterior bellies of the *digastric muscle* and deep to the mandible, in the submandibular fossa. Most of the gland is inferior to the *mylohyoid muscle*, but a deep process extends superior to the muscle. The *submandibular (Wharton) duct* at first runs anteriorly with the deep process and then in close relation to the sublingual gland (first inferior and then medial to it) to reach the *sublingual caruncle* at the summit of which it opens, next to the lingual frenulum.

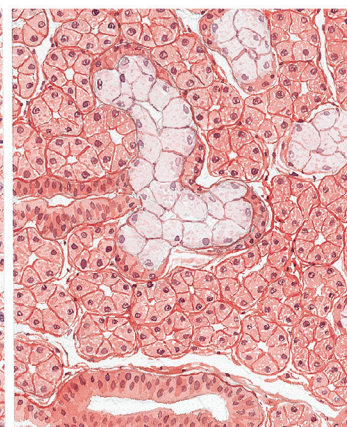
The *sublingual gland*, the smallest of the three paired salivary glands, is located deep to the mucous membrane of the floor of the mouth, where it produces the sublingual fold. It lies superior to the *mylohyoid muscle* in relation with the sublingual fossa on the mandible. In contrast to the parotid and submandibular glands, which have quite definite fibrous capsules, the lobules of the sublingual gland are loosely held together by connective tissue. About 12 *sublingual ducts* leave the superior aspect of the gland and open individually through the mucous membrane of the sublingual fold. Some of the ducts from the anterior part of the gland may combine and empty into the submandibular duct. This is apparently prone to considerable variation.

The nerve supply of the large salivary glands is discussed in a later segment on the innervation of the mouth and pharynx and the autonomic nervous system.

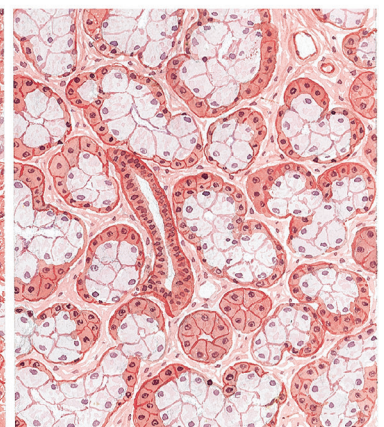
Microscopically, the large salivary glands appear as compound tubular-alveolar glands. The secretions of these glands are serous and mucous and mucous with



Parotid gland:
totally serous



Submandibular gland:
mostly serous, partially mucous



Sublingual gland:
almost completely mucous

serous demilunes, with different proportions of these in different glands. The parotid gland is almost entirely serous, the submandibular gland is predominantly serous but with some mucous alveoli containing serous demilunes, and the sublingual gland varies to quite an extent in composition in different parts of the gland but, for the most part, is predominantly mucous with serous demilunes. In the parotid and submandibular glands, the alveoli are joined by intercalated ducts with low

epithelium to portions of the duct system, which are thought to contribute water and salts to the secretion and, hence, are called secretory ducts. The epithelium of the ducts is at first cuboidal, then columnar, and may finally be stratified cuboidal near the opening of the duct. It should be noted that the appearance of serous demilunes is an artifact of specimen preparation and that during life, the serous-secreting cells of each acinus sit side by side with the mucous-secreting cells.

SECTIONS THROUGH MOUTH AND JAW

AXIAL SECTION AT ATLAS LEVEL AND BEHIND FIRST MOLAR

The structures illustrated and discussed individually in the preceding pages are shown in these cross sections, one axial, the other coronal, in their mutual topographic relationships. The cheek is formed essentially by the *buccinator muscle* and its fascia, with the skin and its appendages, including fat, glands, and connective tissue, covering it on the outside and the oral mucosa on the inside.

The continuity of the oral and oropharyngeal wall, as it becomes visible in this cross section, may attain some practical significance in abscess formation and other pathologic processes. One should realize that the buccinator muscle is separated only by the small fascial structure, the *pterygomandibular raphe*, from the *superior pharyngeal constrictor muscle*, which constitutes the most substantial component of the oropharyngeal wall. The thin *pharyngeal fascia*, created by the looseness of its structure a retropharyngeal space, separates the posterior wall of the pharynx from the vertebral column and prevertebral muscles.

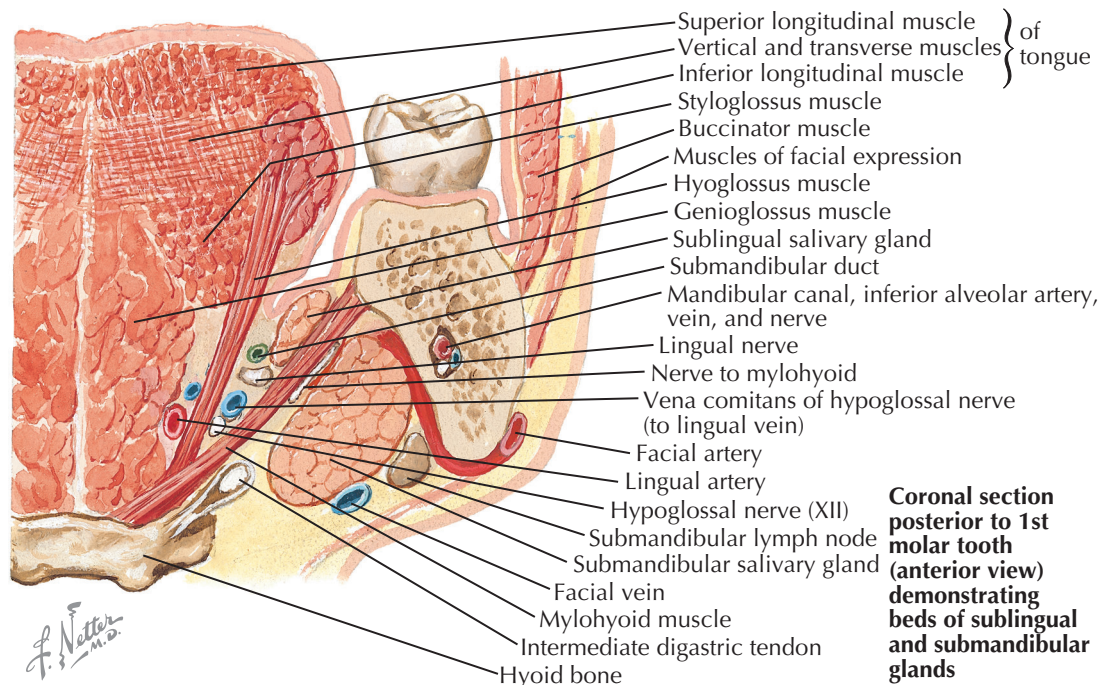
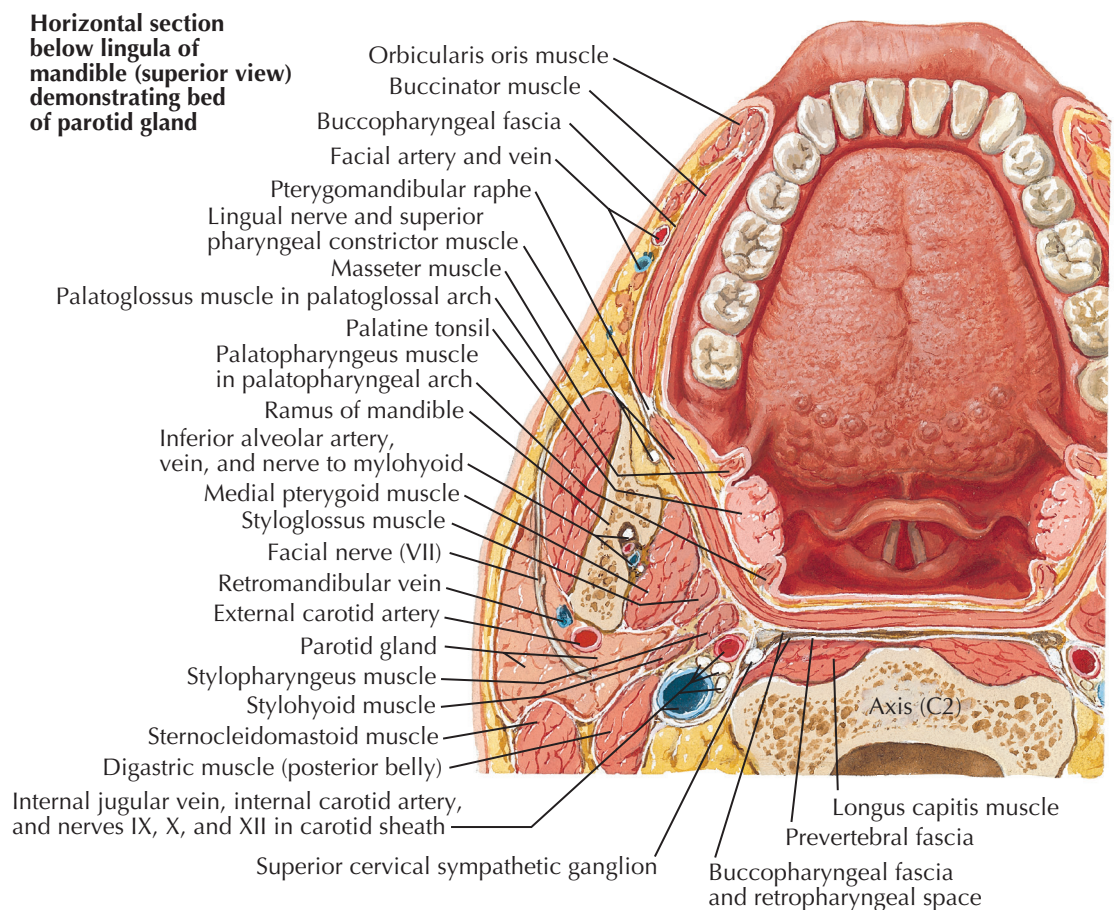
The tonsillar bed, as it lies between the *palatoglossal* and *palatopharyngeal arches*, is easier to comprehend in a cross section.

Supplementing the picture of the external aspect of the *parotid gland*, the cross section demonstrates the thin medial margin of the gland and its relation to the muscles arising from the styloid process (*stylohyoid*, *stylopharyngeus*, and *styloglossus muscles*), the *internal jugular vein*, and the *internal carotid artery*. Of further note is the closeness of the most medial part of the parotid gland to the lateral wall of the pharynx and the location within the glandular substance of the *retromandibular vein* (beginning above the level of the cross section by the confluence of the *superficial temporal* and *maxillary veins*), the *facial nerve*, and the *external carotid artery*, which latter divides higher up, but still within the gland, into the *superficial temporal* and *maxillary arteries*.

CORONAL SECTION

The frontal or coronal section of the tongue brings into view the mutual relationships of its muscular components, particularly the *lingual septum* dividing the tongue into symmetric halves. The *lingual artery* courses medial to the *genioglossus muscle*, whereas the main *lingual vein*, the *hypoglossal* and *lingual nerves*, and the *duct of the submandibular gland* lie lateral to the *genioglossus* and medial to the *mylohyoid muscle*. Located inferior and lateral to the latter muscle is the main body of the *submandibular gland*. Its lateral margin touches the

Horizontal section below lingula of mandible (superior view) demonstrating bed of parotid gland



mandible, only separated from it at the level of the section by the *facial artery*. On the deep surface of the *mylohyoid muscle* one also finds the posterior end of the *sublingual salivary gland* in a location that would be occupied by the deep process of the *submandibular gland* in a section slightly more posteriorly. As the result of the crossings of the *lingual nerve* and *submandibular duct*, the apparent relationship of these two structures in the cross section would be reversed if one were to obtain a more anterior section.

The *mandibular canal* harbors the *inferior alveolar artery, vein, and nerve*. The *intermediate tendon of the digastric muscle* passes through the fascial loop that anchors it to the *hyoid bone*.

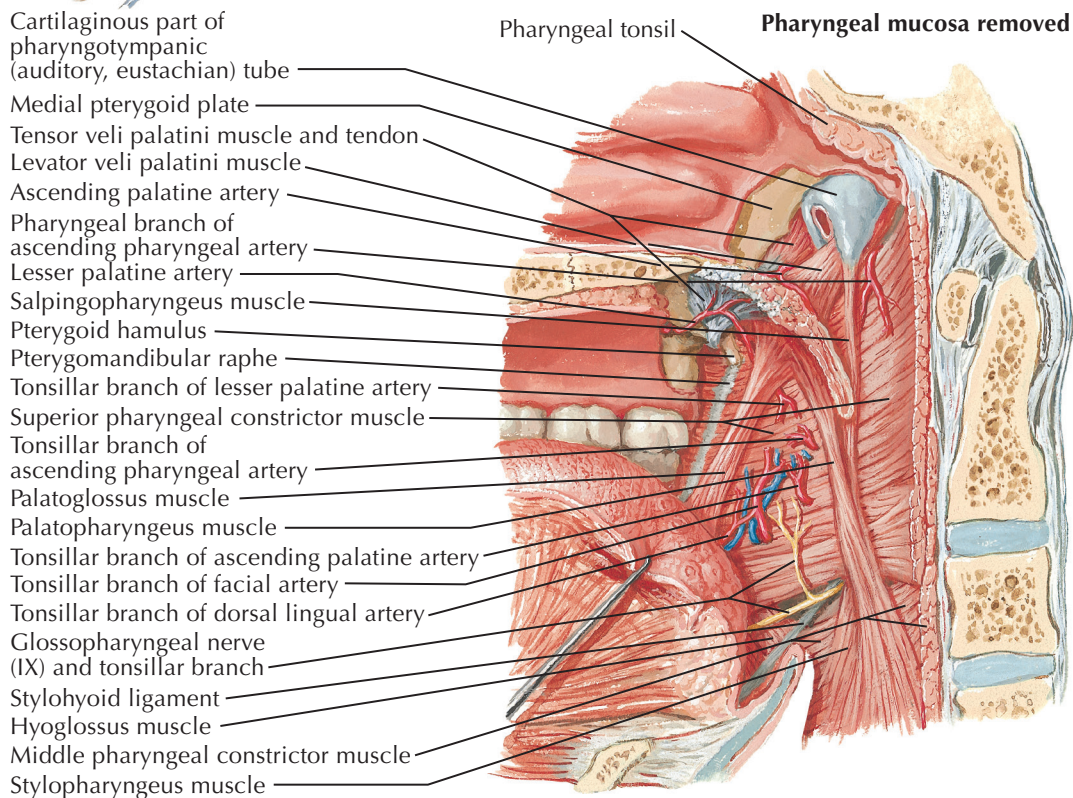
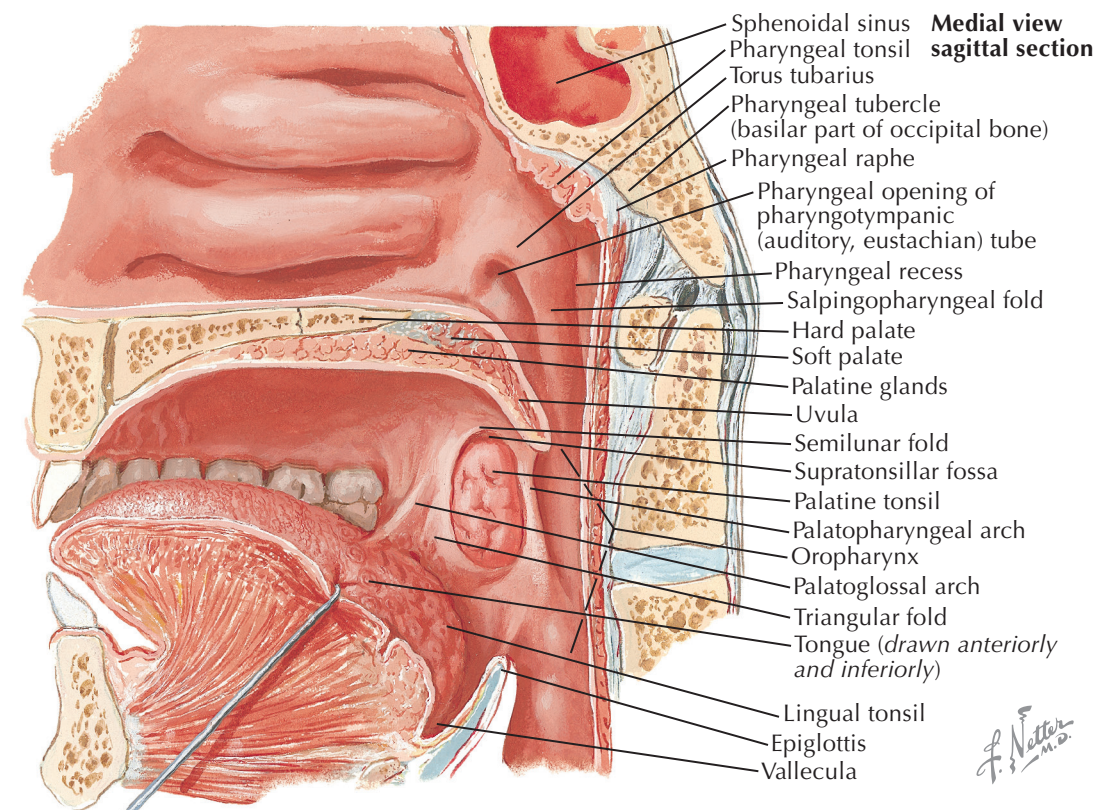
With the two reflections—one from the inferior surface of the tongue across the floor of the mouth to the gum on the inner aspect of the alveolar process of the mandible, the other from the outer surface of this process to the cheek—the lining of the oral cavity by the mucous membrane becomes continuous.

FAUCES

The connotation given to the term *fauces* varies. Though complete agreement exists as to the general region to which the term refers, the precise contents and boundaries of this region vary between sources. In general, the area covers the space from the oral cavity into the pharynx. By most authors, the designation *isthmus of the fauces*, or oropharyngeal isthmus, is taken to mean the aperture by which the mouth communicates with the pharynx (i.e., the dividing line between the oral cavity and the oropharynx). The boundaries of this isthmus are the soft palate superiorly, the dorsum of the tongue in the region of the terminal sulcus inferiorly, and the left and right *palatoglossal folds*, also known as the anterior pillars of the fauces, which rise archlike on each side in the posterior limit of the oral cavity.

Closer to the oropharynx, a second arch is formed by the *palatopharyngeal folds*, also called the posterior pillars of the fauces. As a result of the projecting prominence of the anterior and posterior folds on each side, a fossa (tonsillar fossa or tonsillar sinus) comes into existence, which houses the *palatine tonsil*. On the free surface of this oval mass, which may bulge medially into the cavity of the pharynx for varying distances, 12 to 15 orifices (fossulae tonsillares) can be recognized. These are the openings of the tonsillar crypts. The latter branch and extend deeply into the substances of the tonsils. Several quite variable folds may overlap the medial surface of the tonsils in different degrees. Most frequently found is a *triangular fold* located anteriorly and inferiorly to the tonsils. Also, between the superior portions of the palatoglossal and palatopharyngeal folds, one may encounter frequently a supratonsillar fold that contains tonsillar tissue, a fact that has prompted some authors to call the recess below this fold the infratonsillar recess (or fossa) and others to designate it as "supratonsillar." The lateral surface of the tonsil has a fibrous capsule, which is separated by some loose connective tissue from the *superior constrictor muscle* of the pharynx and, to a lesser and variable degree, from the *palatopharyngeus muscle* that sits deep to the fold of the same name.

The chief blood supply of the tonsil is the *tonsillar branch of the facial artery*, but the tonsillar branches of the *lesser palatine*, *ascending palatine*, *ascending pharyngeal*, and *dorsal lingual arteries* also participate in the arterial



blood supply. Lymphatic fluid from the tonsil drains primarily to the *jugulodigastric lymph node* of the *superior deep cervical group*. The tonsil is innervated primarily by the *glossopharyngeal nerve*, though a few branches of the lesser palatine nerves also enter the tonsils.

A stratified squamous epithelium covers the tonsil and also lines the crypts, where it may be obscured by lymphocyte infiltration. The mass of the tonsils consists of lymphatic (lymphoid) tissue, which presents itself

mostly in the form of *lymph nodules* or follicles, which, particularly in younger individuals, contain many germinal centers. Expansions from the above-mentioned fibrous capsule on the lateral tonsillar surface enter the lymphoid tissue, forming septa between the follicles surrounding the adjacent crypts.

Present at birth and increasing in size rapidly during the first few years of life, the tonsils usually decrease in size about puberty and may become atrophic in old age.

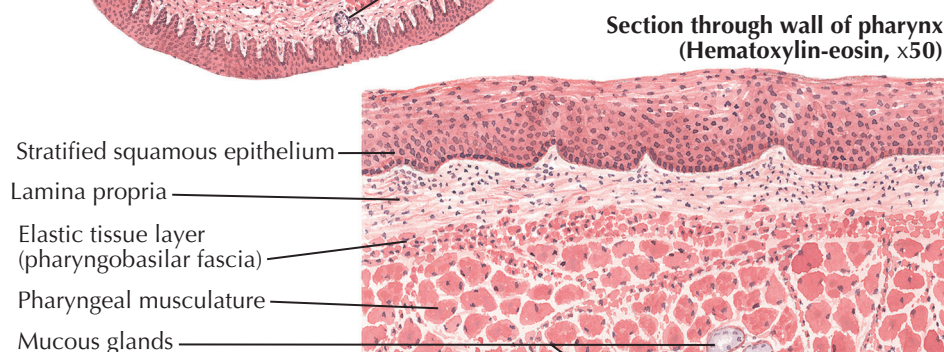
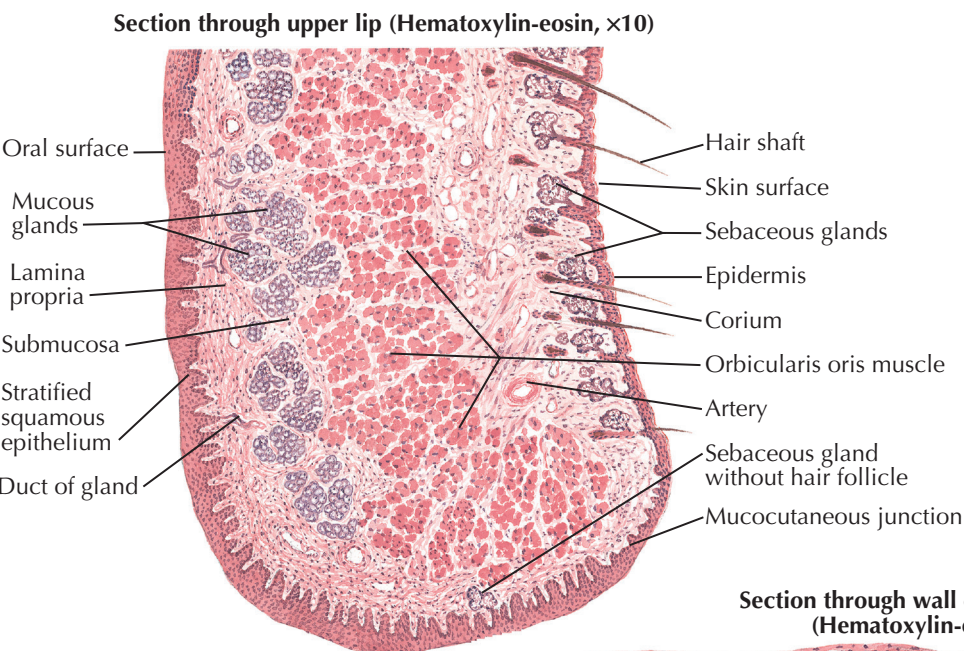
HISTOLOGY OF MOUTH AND PHARYNX

The mouth and pharynx are lined by a mucous membrane that is attached in much of the area to the supporting wall (bone, cartilage, or skeletal muscle) by a fibroelastic, gland-containing submucosa that varies greatly in size, looseness, and the distinctness with which it can be delimited from the mucous membrane. The submucosa is interpreted as absent on most of the hard palate, the gums, and the dorsum of the tongue. The mucous membrane is composed of epithelium, which is predominantly nonkeratinized, stratified, and squamous in type, a basement membrane, and the fibroelastic lamina propria, which has vascular papillae indenting the epithelium to varying degrees in different areas. The muscularis mucosae, which is present in the digestive tube in general, is missing in the mouth and pharynx. Its place is occupied by an elastic network in the pharynx.

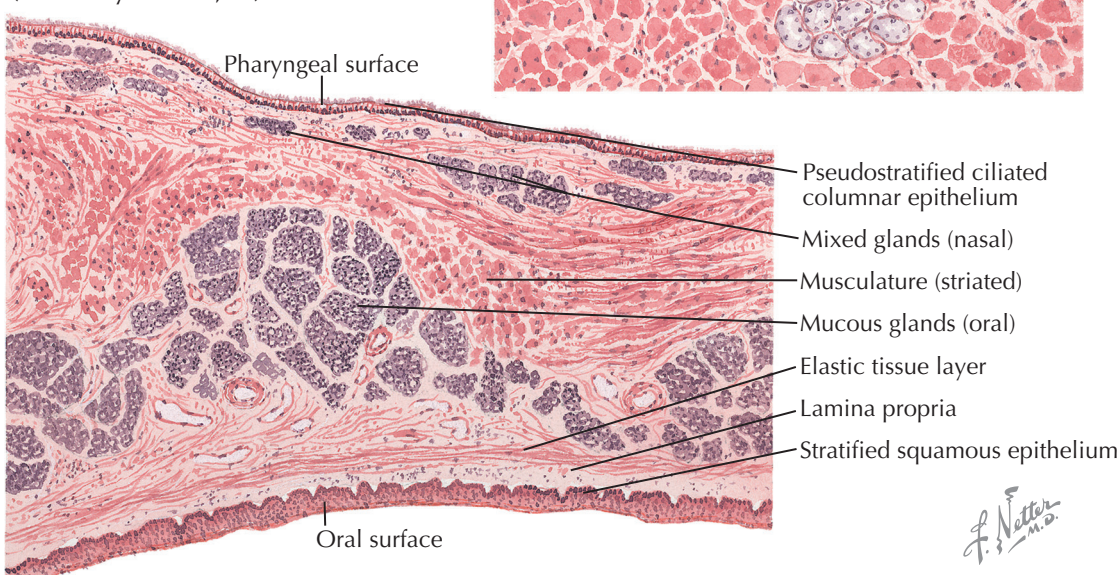
The *lip* has a framework of skeletal muscle, chiefly the *orbicularis oris muscle*. External to this are typical subcutaneous tissue and skin with hair follicles, sebaceous glands, and eccrine sweat glands. On the inner side of the muscular framework is the submucosa containing rounded groups of mixed, predominantly *mucous glands* (labial glands). The *submucosa* is not definitely delimited from the covering mucous membrane, which is composed, as described above, of *lamina propria* and nonkeratinized, *stratified, squamous epithelium*. The free margin of the lip has its characteristic red (or vermilion) color because the epithelial cells contain much translucent eleidin, and the vascular papillae of the tunica propria indent the epithelium more deeply here. The blood in the capillaries thus shows through to a greater extent.

The general structure of the cheek is very similar to that of the lip, the muscular framework being formed by the buccinator muscle. Here some glands are external to the muscular framework. In most of the lip and the cheek, the mucous membrane is quite closely bound to the muscular framework, preventing large folds of mucous membrane from being formed that might be easily bitten. Near the continuity of the mucous membrane with the gums, the attachment is much looser to allow for freedom of movement.

The *soft palate* has a fibromuscular framework, with the fibrous constituents (the expansion of the tendons of the tensor veli palatini muscles) being more prominent near the hard palate. On each side of the framework is a mucous membrane. That on the oral side has an elastic layer separating the lamina propria from a much thicker submucosa containing many glands. The *epithelium* is the typical nonkeratinized, *stratified, squamous* variety, which rounds the free margin of the soft palate and extends for a variable distance onto the pharyngeal surface.



Section through soft palate (Hematoxylin-eosin, ×7)



The *wall of the pharynx* is for the most part composed of a mucous membrane, muscular layer, and thin fibrous sheath outside of the muscle that attaches the pharynx to adjacent structures. The *epithelium* in the nasopharynx (except for its lowest portion) is pseudostratified, ciliated, and columnar, whereas that of the rest of the pharynx is nonkeratinized, *stratified*, and *squamous*. The *lamina propria* is fibroelastic, with scattered small papillae indenting the epithelium. The

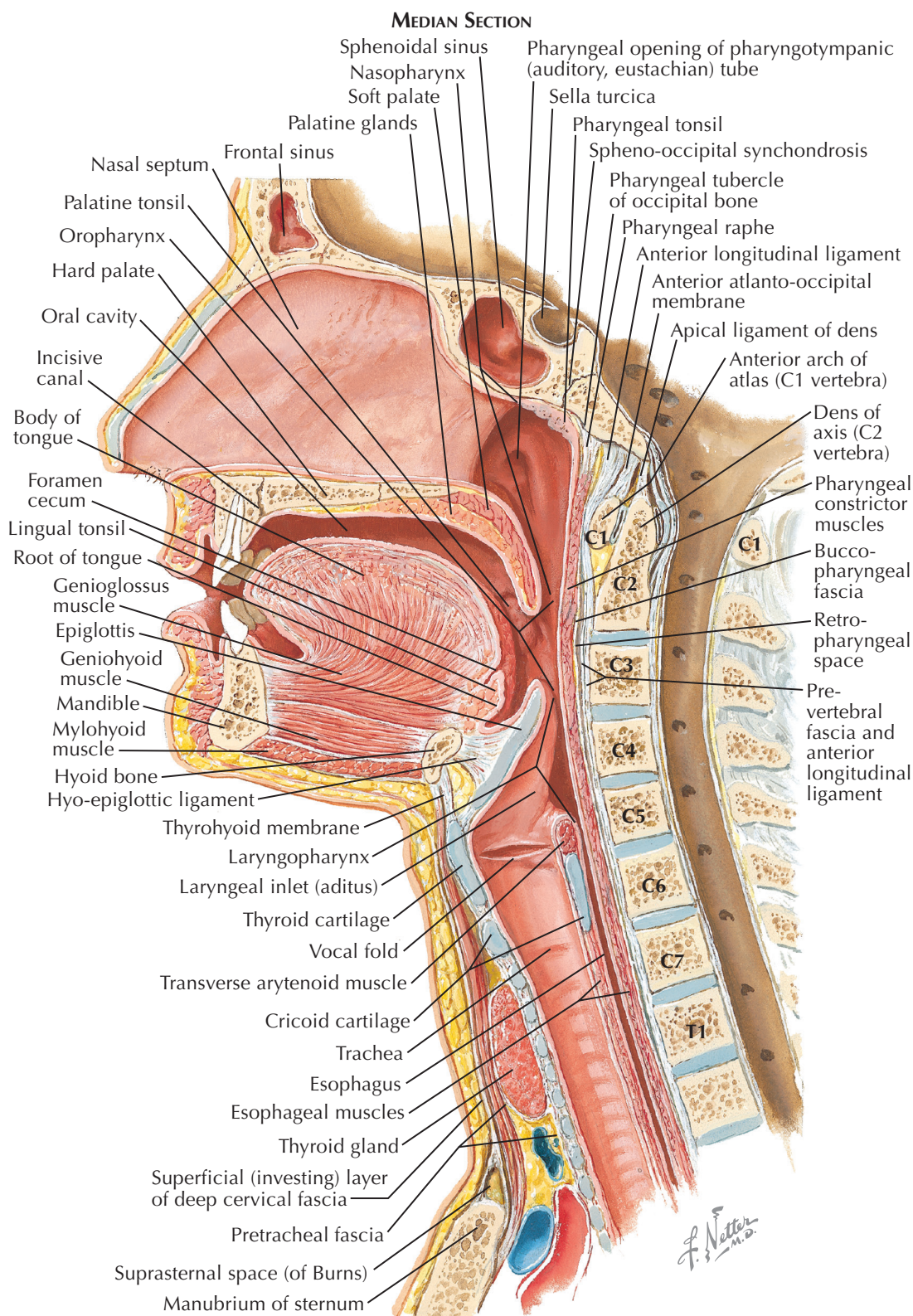
deepest part of this lamina is a definite *elastic tissue layer* with many longitudinally oriented fibers. A well-developed submucosa is present only in the lateral extent of the nasopharynx and near the continuity of the pharynx with the esophagus. Scattered *seromucous glands* are present, mostly where there is pseudostratified columnar epithelium. The muscular layer, made up of skeletal muscle, is present as somewhat irregularly arranged layers.

PHARYNX

The pharynx is a musculomembranous tube; much of its anterior wall is absent due to the fact that the right and left nasal cavities, oral cavity, and larynx open into its anterior side. It extends from the base of the skull to the inferior border of the cricoid cartilage at the level of the lower margin of the sixth cervical vertebra, at which time it becomes continuous with the esophagus. In addition to the cavities already listed, the pharynx also communicates with the middle ear on each side by means of the *auditory (eustachian) tube*; this fact explains how infections spread from the pharynx to the middle ear, making a total of seven cavities with which it has communication. The transverse diameter of the pharynx exceeds the anteroposterior diameter, which is greatest superiorly and is diminished to nothing inferiorly where the anterior and posterior walls are in contact unless separated during the act of swallowing. The transverse diameter does not differ greatly throughout the length of the pharynx, except where it narrows at the lower end.

The posterior wall of the pharynx is attached superiorly to the *pharyngeal tubercle* on the inferior surface of the basilar part of the occipital bone, its adjacent area, and the undersurface of the petrous portion of the temporal bone medial to the external aperture of the carotid canal. The lateral wall has several attachments. It is attached superiorly to the cartilaginous portion of the auditory tube, which pierces the wall in this area. Anteriorly it connects to the lower, posterior border of the medial pterygoid plate and its hamulus, as well as the *pterygomandibular raphe*, the inner surface of the mandible (near the posterior end of the mylohyoid line), the side of the root of the tongue, the hyoid bone, and finally the thyroid and cricoid cartilages. Inferiorly, the walls of the pharynx continue as the walls of the esophagus.

The pharyngeal lining is a mucous membrane that is continuous with the lining of the cavities communicating with the pharynx. External to the mucous membrane of the posterior and lateral walls is a sheet of fibrous tissue, more defined superiorly than inferiorly, known as the pharyngeal aponeurosis (*pharyngobasilar fascia*), and external to this is the muscular layer of the pharynx. On the outer surface of the muscular layer is another fascial covering, the buccopharyngeal fascia.



The posterior pharyngeal wall is separated from the prevertebral fascia overlying the anterior arch of atlas and the bodies of the second to the sixth cervical vertebrae (partially covered by the longus colli and longus capitis muscles) by a minimal amount of loose fibrous connective tissue. This allows the pharynx some degree of freedom of movement and forms a *retropharyngeal space*. Under anesthesia it is possible to palpate these bony structures as far caudally as the fourth or fifth cervical vertebra.

On the basis of openings in its anterior wall, the pharynx is divided into the *nasopharynx*, *oropharynx*, and *laryngopharynx*. The nasopharynx typically has a purely respiratory function (acting as a passageway for air and not for food) and remains patent because of the bony framework to which its walls are related. The anterior wall is entirely occupied by the *choanae* (posterior nares), with the posterior border of the *nasal septum* between them. The posterior wall and roof form a continuous arched wall, with the roof extending from the

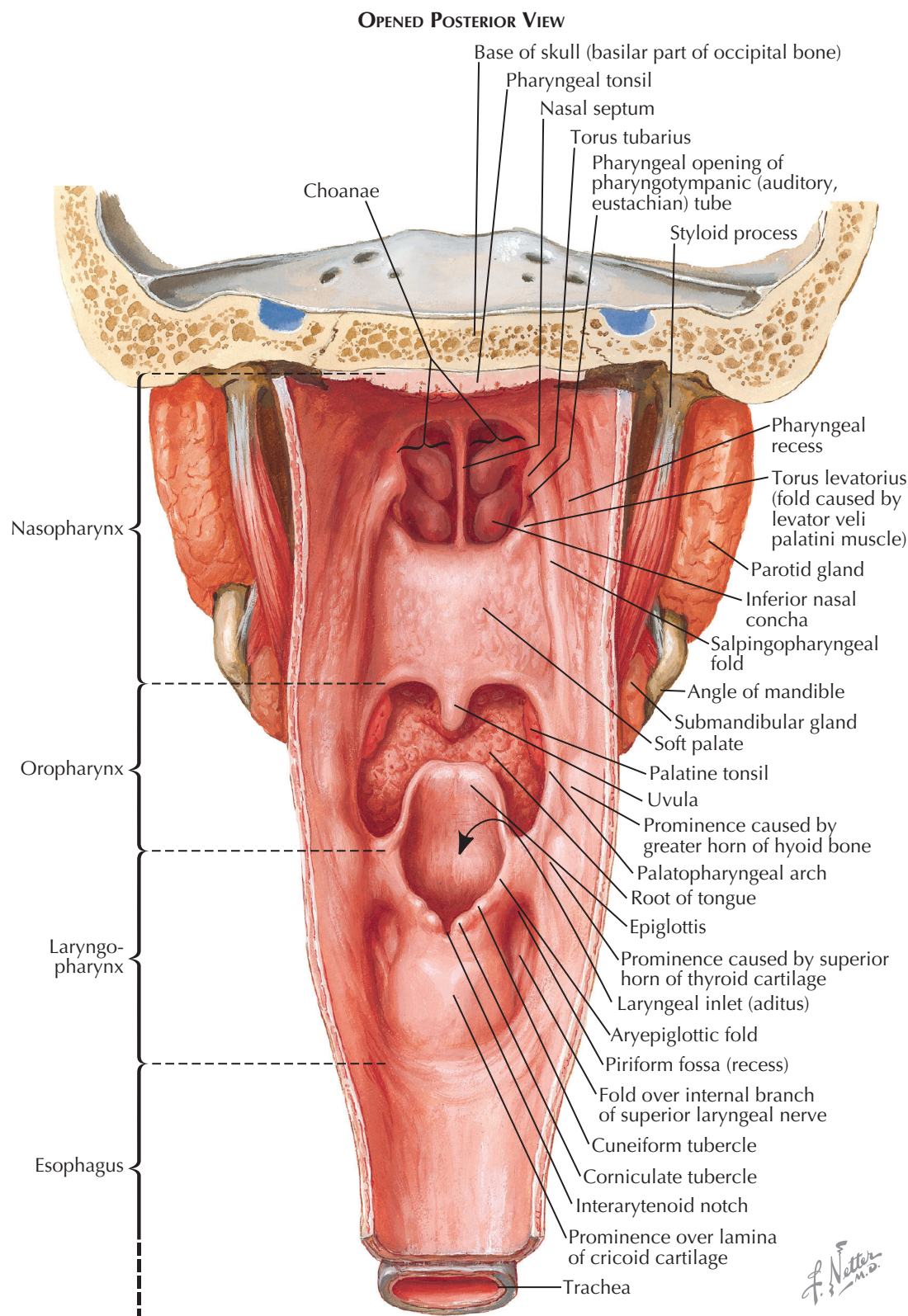
PHARYNX (Continued)

superior margin of the choanae (where it is continuous with the roof of the nasal cavities) to about the midpoint of the basilar portion of the occipital bone; the posterior wall extends from this point caudally to about the lower border of the anterior arch of the atlas. In the region where the roof and posterior wall meet, the mucous membrane is thrown into many variable folds, with an accumulation of nodular and diffuse lymphoid tissue (extensively developed in children, atrophied in adults) forming the *pharyngeal tonsil* (adenoids). In the midline, near the anterior margin of the pharyngeal tonsil, is a minute flask-shaped depression of mucous membrane, known as the pharyngeal bursa. Also in the midline, near the anterior limit of the roof, and submerged in the mucosa or lying in the periosteum, a microscopic remnant of the Rathke pouch (pharyngeal hypophysis) can be found, which is grossly visible only when it has become cystic or has formed a tumor.

The incomplete floor of the nasopharynx is formed by the posterosuperior surface of the *soft palate* with an opening from the nasal to the oral pharynx between the soft palate and the posterior wall of the pharynx. This opening is closed by bringing these two structures in contact.

On the lateral wall of the nasopharynx at the level of the inferior concha is the *pharyngeal opening* of the auditory tube, with the *pharyngeal recess* (fossa of Rosenmüller) posterior to it. The levator cushion (produced by the levator veli palatini muscle) bulges into the inferior margin of the triangular opening, and coursing inferiorly from the posterior lip is the *salpingopharyngeal fold* produced by the muscle of the same name. In childhood, a considerable mass of lymphoid tissue (tubal tonsil) may be present around the opening of the auditory tube and may enlarge, blocking drainage from the middle ear.

The *oropharynx* extends from the inferior border of the nasopharynx to the level of the pharyngoepiglottic folds, with the *epiglottis* protruding into it. This part of the pharynx carries both air and food. The posterior wall remains in relation to the bodies of the second to fourth cervical vertebrae, whereas the anterior wall is deficient superiorly where the oropharynx and oral cavity communicate by means of the isthmus of the



fauces. Inferior to the isthmus, the anterior wall is formed by the posterior third of the tongue. Between the tongue and epiglottis are the valleculae, spaces where foreign bodies may lodge.

The *laryngopharynx* lies posterior to the larynx and anterior to the fifth and sixth cervical vertebrae. The superior part of the anterior wall contains the roughly triangular *laryngeal inlet (aditus)*, the borders of which are formed by the margins of the epiglottis, the *aryepiglottic folds*, and the *interarytenoid incisure*. Inferior to the

laryngeal opening, the laryngopharynx only transmits food and is purely alimentary in function. The mucous membrane of the anterior wall overlies the posterior surfaces of the arytenoid cartilages and the lamina of the *cricoid cartilage* (mostly covered by laryngeal muscles). Inferior to the laryngoepiglottic fold on each side is the *piriform recess*, located between the cricoid and arytenoid cartilages medially and the lamina of the thyroid cartilage laterally. This is another location where foreign bodies may lodge.

BONY FRAMEWORK OF MOUTH AND PHARYNX

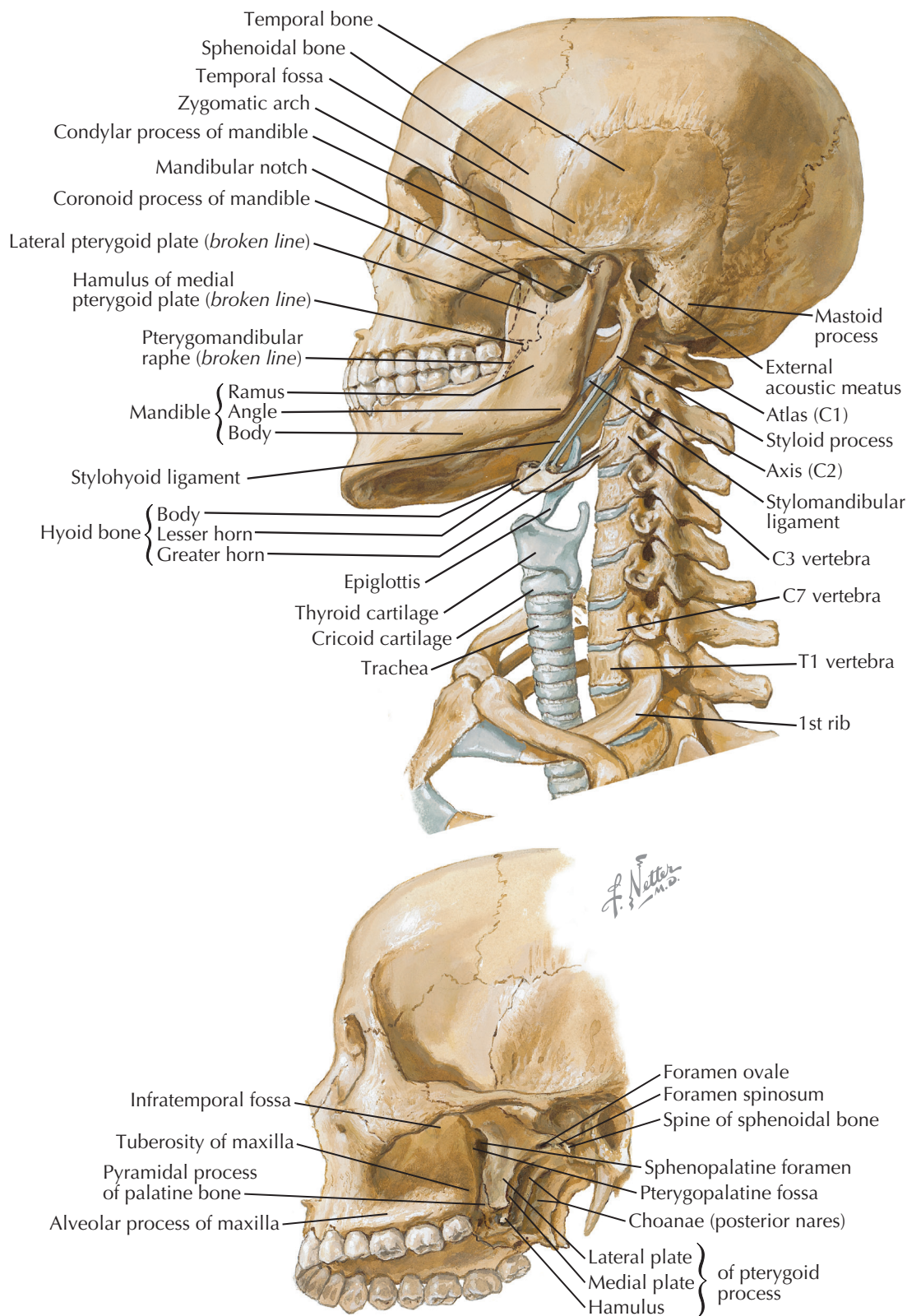
The bony framework of the mouth is composed largely of the two *maxillae*, immovably attached to other bones of the skull, and the mobile *mandible*. The portions of the maxillae contributing to the formation of the bony palate have been previously described, and the alveolar processes of the maxilla have been referred to as providing the sockets for the upper teeth. Other bony structures contributing to the framework of the mouth and pharynx, serving as attachments for muscles of the mouth and pharynx, are parts of the *palatine*, *sphenoid*, *temporal*, *occipital*, and *hyoid bones* as well as the *zygomatic arch*.

The palatine bone is interposed between the maxilla and the *pterygoid process* of the sphenoid bone, and its horizontal portion forms the framework of the posterior part of the hard palate. Its pyramidal process articulates with the lower portions of the medial and lateral pterygoid laminae and helps to complete the pterygoid fossa.

The sphenoid bone is located in the base of the skull posterior to the ethmoid, frontal, palatine, and maxillary bones. It is anterior to the occipital and temporal bones, and it has the right and left *pterygoid processes* extending inferiorly from its body. Each pterygoid process has a *medial* and *lateral pterygoid plate*, with a *pterygoid hamulus* projecting posterolaterally from the medial pterygoid plate, to which the *pterygomandibular raphe* attaches and around which the tendon of the tensor veli palatini muscle passes. The greater wing of the sphenoid forms the anterior parts of the *temporal* and *infratemporal fossae*. The *spine of the sphenoid*, to which the sphenomandibular ligament attaches, is just medial to the mandibular fossa of the temporal bone.

The *external acoustic meatus* is an obvious landmark in the temporal bone that extends toward the middle ear. Posterior to the meatus is the *mastoid process*, on the medial side of which is the mastoid notch, where the posterior belly of the digastric muscle attaches. Antero-inferior to the meatus is the mandibular fossa for the articulation with the condyle of the mandible. Inferior to the meatus and posterior to the mandibular fossa is the *styloid process*, which projects for a variable distance inferiorly and slightly anteriorly. The squamous portion of the temporal bone is the extensive flat portion of the bone superior to the meatus that, together with parts of the greater wing of the sphenoid, frontal, and parietal bones, forms the temporal fossa for the attachment of the temporalis muscle. The petrous portion of the temporal bone extends medially and somewhat anteriorly from the meatus to insinuate itself between the basilar portion of the occipital bone and the infratemporal portion of the greater wing of the sphenoid.

The *zygomatic arch* forms a buttress over the infratemporal fossa and gives origin to the masseter muscle. It is made up (from front to back) by the zygomatic process of the maxilla, the zygomatic bone, and the zygomatic process of the temporal bone.



The basilar portion of the occipital bone is posterior to the body of the sphenoid bone and forms the bony framework of the roof and the superior part of the posterior wall of the pharynx. The pharyngeal tubercle on the inferior surface of the basilar portion of the occipital bone, anterior to the foramen magnum, is the superior attachment of the median raphe of the pharynx.

The hyoid bone has a body, as well as a greater and lesser horn on each side. It is a key structure in the floor

of the mouth (and related tongue) and is important in the movements of these structures through the muscles that attach to it. The hyoid bone is also important as the origin of the middle pharyngeal constrictor muscle.

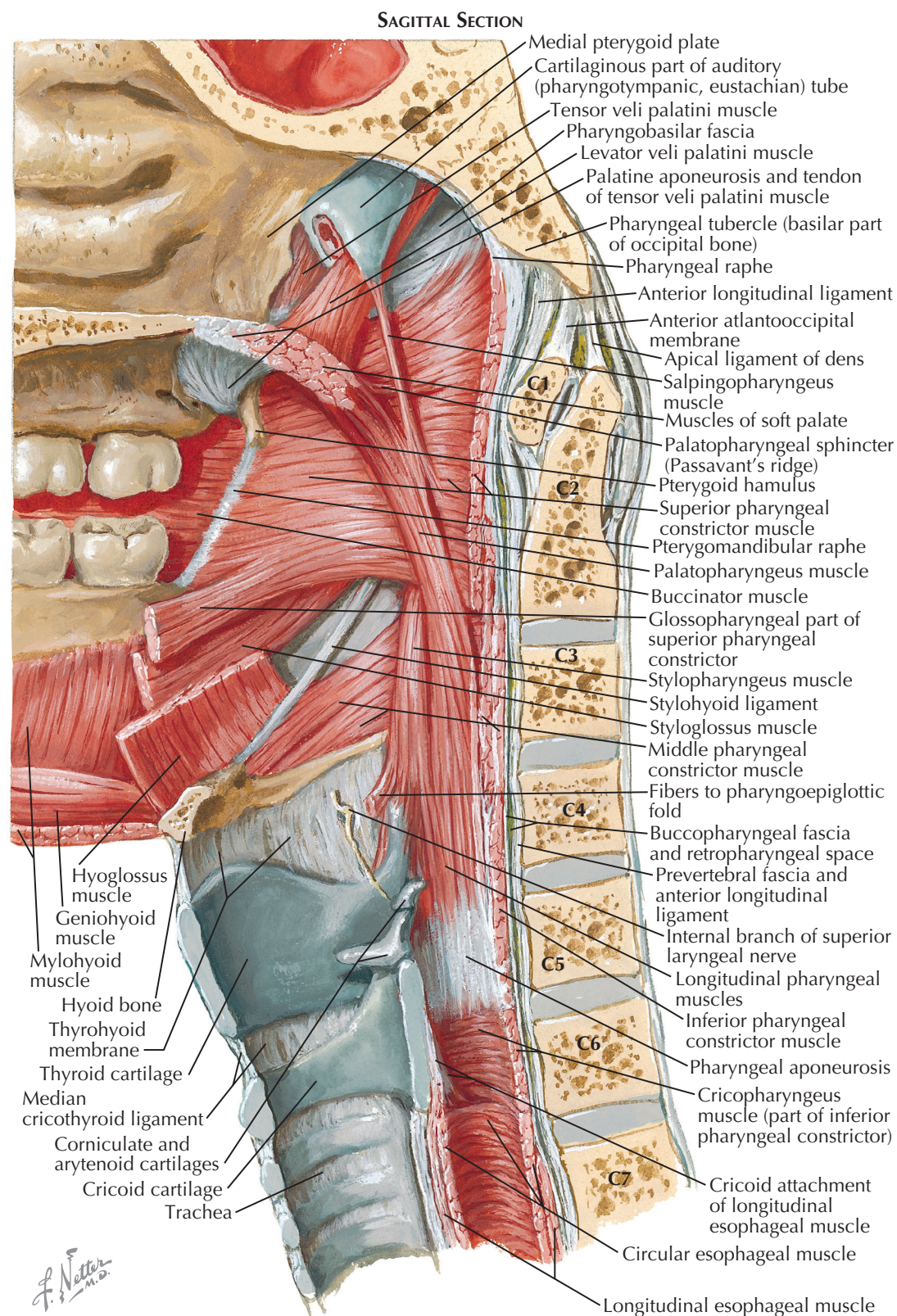
Supplementing the bony framework in supplying attachments to the muscles of the pharynx are the thyroid and cricoid cartilages that give origin to the inferior pharyngeal constrictor and some insertion to the stylopharyngeus muscle.

MUSCULATURE OF PHARYNX

Much of the framework of the lateral and posterior walls of the pharynx is formed by an outer and inner layer of musculature. These layers are not completely separable throughout, because in some places they are definitely intermingled and overlap. The outer layer is more nearly arranged in a circular fashion and is made up of the three constrictor muscles of the pharynx, designated as superior, middle, and inferior pharyngeal constrictors, which overlap each other. The inner layer, which falls far short of being a complete layer, is longitudinally arranged and is composed of the stylopharyngeus, palatopharyngeus, and salpingopharyngeus muscles plus some other variable and irregular bundles of muscle fibers.

The *superior pharyngeal constrictor muscle* is quadrilateral in shape and somewhat thin. It originates from the posteroinferior edge of the medial pterygoid plate, the hamulus of the medial pterygoid plate, the pterygomandibular raphe (which runs from the hamulus to the lingula of the mandible), the posterior one fifth or so of the mylohyoid line and the adjacent part of the alveolar process of the mandible, and the side of the root of the tongue (the glossopharyngeus muscle). From this extensive line of origin, the fibers course posteriorly, with the lower fibers passing somewhat inferiorly and medially to meet the ones from the opposite side in the median *pharyngeal raphe*. This raphe extends most of the length of the posterior wall of the pharynx, being attached superiorly to the *basilar part of the occipital bone* at the *pharyngeal tubercle*, to which the uppermost fibers of the superior constrictor are also attached. The curved upper edge of the muscle passes deep to the auditory tube and is thus separated by a short distance from the base of the skull except at the midline posteriorly. At this gap the only framework of the pharynx is the *pharyngobasilar fascia*. The *buccinator muscle* runs anteriorly from the pterygomandibular raphe, which serves as part of its origin, and this muscle and the superior constrictor thus form a continuous sheet, which is therefore the continuous framework of the lateral wall of the oral and oropharyngeal cavities. A slip of the superior part of the superior constrictor muscle blends into the palatine aponeurosis, forming the so-called *palatopharyngeal sphincter*; contraction of which produces a ridge (Passavant ridge) against which the soft palate is raised. A triangular gap filled with fibrous connective tissue can be noted between the lower border of the superior pharyngeal constrictor muscle, the posterior border of the *hyoglossus muscle*, and the upper border of the middle pharyngeal constrictor muscle. The stylopharyngeus muscle inserts into this gap between the superior and middle constrictors. The *stylohyoid ligament* and *glossopharyngeal nerve* also cross this gap.

The *middle pharyngeal constrictor muscle* has a V-shaped line of origin, with the V resting on its side and the angle pointing anteriorly. The superior arm of this V is formed by the terminal portion of the *stylohyoid ligament* and the lesser horn of the *hyoid bone*, whereas

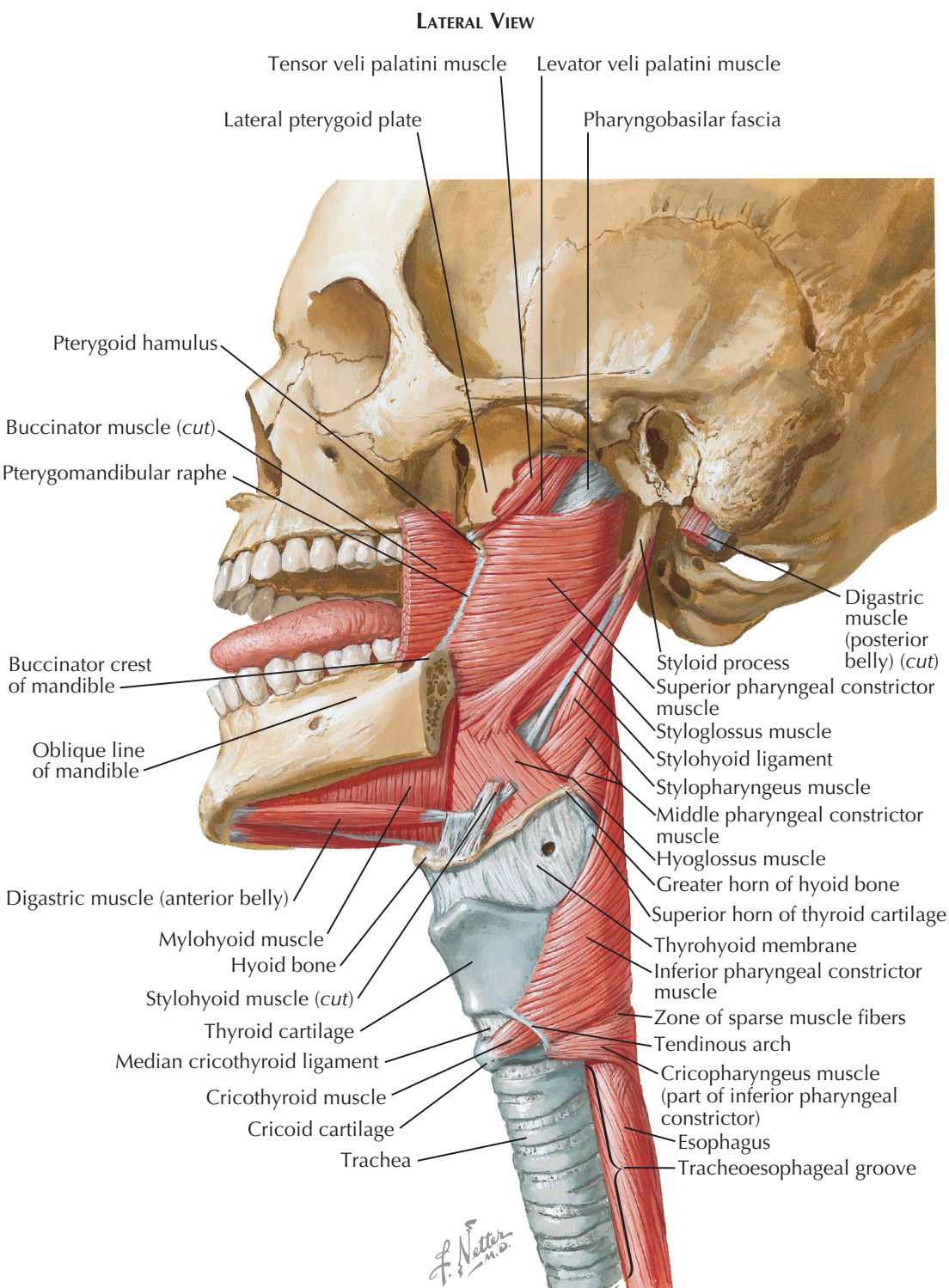


the inferior arm of the V is formed by the entire length of the greater horn of the hyoid bone. From this rather narrow origin the fibers fan out widely, with the upper fibers coursing superiorly while curving posteriorly and medially. The middle fibers course horizontally and curve posteriorly and medially. The inferior fibers course inferiorly and curve posteriorly and medially. The medial pharyngeal constrictor's superior fibers overlap the superior constrictor, and the inferior fibers

are overlapped by the inferior constrictor and reach quite far inferiorly in the posterior wall of the pharynx, to about the level of the superior border of the cricoid cartilage. The middle constrictor's fibers fuse and blend with those of the other side in the median raphe. Between the lower border of the middle constrictor and the upper border of the inferior constrictor, a triangular gap is noted, which is bounded anteriorly by the thyrohyoid muscle.

MUSCULATURE OF PHARYNX (Continued)

The *inferior pharyngeal constrictor muscle* is relatively thick and strong. It arises from the oblique line of the thyroid cartilage and the area just dorsal to that line, from a tendinous arch extending from the inferior end of the oblique line of the thyroid cartilage to the lateral surface of the cricoid cartilage. That portion arising from the cricoid cartilage is frequently referred to as the *cricopharyngeus muscle*. As do the other constrictor muscles, the inferior constrictor passes posteriorly and then medially to blend with its counterpart at the pharyngeal raphe. The cranial fibers pass more and more obliquely as they approach the raphe and overlap the middle constrictor, reaching nearly as far superiorly as the middle constrictor does. The fibers of the cricopharyngeus portion of the muscle course horizontally and form an annular bundle with no median raphe. It does blend to some extent with the related circular fibers of the esophagus, being referred to by some as the superior esophageal sphincter. A zone of sparse musculature is present between the cricopharyngeus muscle and the rest of the inferior constrictor muscle, which creates a weaker area in the posterior wall of the pharynx, where an instrument may accidentally pierce the wall. Just below the inferior border of the cricopharyngeus muscle, a triangular area (sometimes called the Laimer triangle) occurs in which the posterior wall of the esophagus is variably deficient, because the longitudinal muscle fibers of the esophagus tend to diverge laterally and pass around the esophagus to attach on the cricoid cartilage. It is thus seen that there is more than one weakened area in the posterior wall of the general region of the pharyngoesophageal junction, where diverticula may occur. The recurrent laryngeal nerve and accompanying inferior laryngeal vessels pass deep



to the inferior constrictor muscle to travel superiorly behind the cricothyroid joint in entering the larynx.

As their names indicate, the major action of the superior, middle, and inferior pharyngeal constrictor muscles of the pharynx is to constrict the pharynx. They contract in sequence, grasping the bolus of food as it passes from the mouth to the esophagus. The nerve supply of the constrictor muscles of the pharynx is derived from the pharyngeal plexus.

The *stylopharyngeus muscle* is long, slender, and cylindrical superiorly but flattens near its insertion. It origi-

nates from the medial aspect of the base of the *styloid process* and then passes inferiorly and anteriorly, going between the external and internal carotid arteries and then entering the wall of the pharynx in the interval between the superior and middle constrictor muscles. As it spreads out internal to the middle constrictor muscle, the greater horn of the hyoid bone, and the thyrohyoid membrane, some of its fibers join the palatopharyngeus muscle and insert on the superior and posterior borders of the thyroid cartilage. Some fibers pass into the pharyngoepiglottic fold, and they are

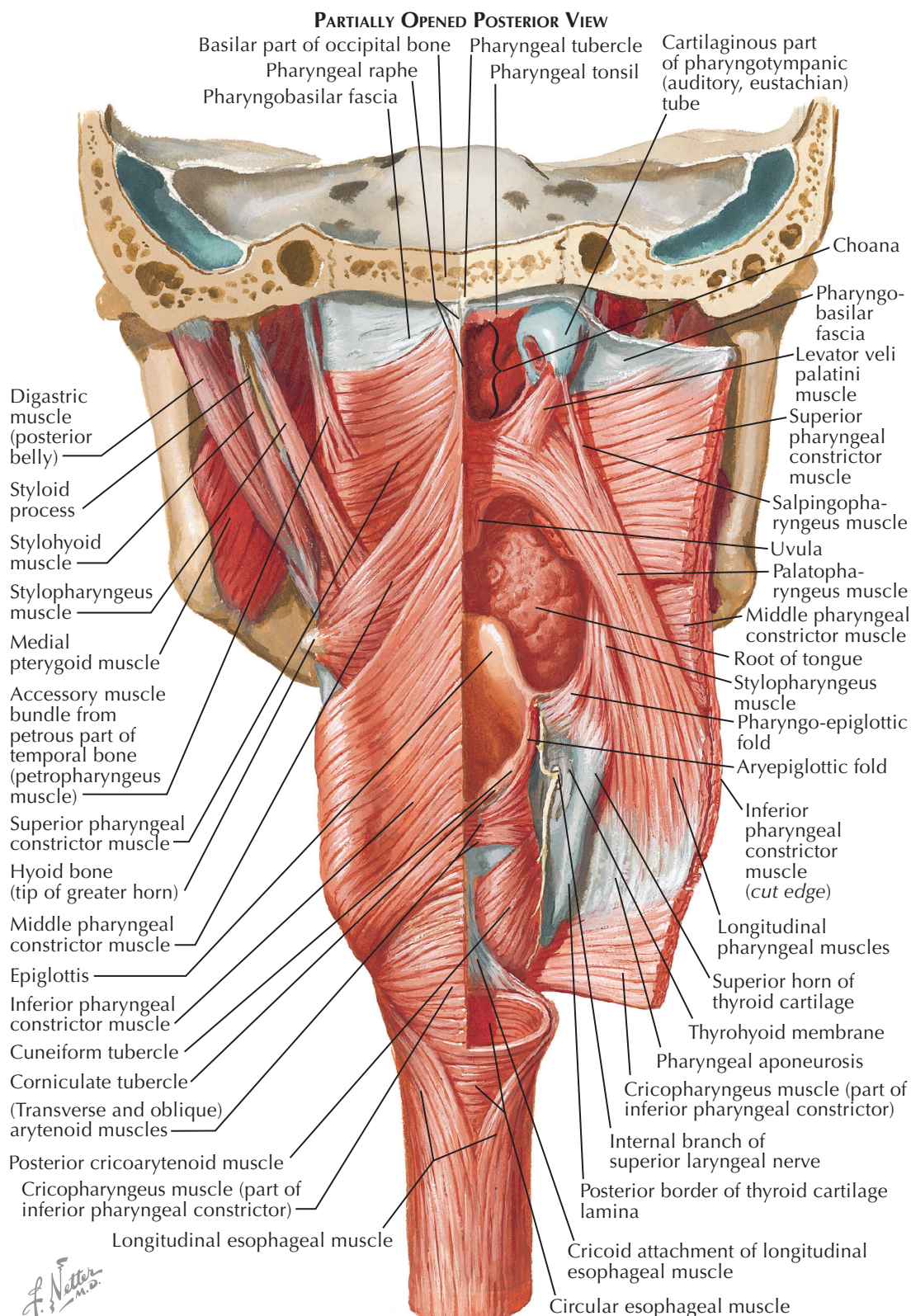
MUSCULATURE OF PHARYNX

(Continued)

primarily responsible for the production of this fold. The remaining fibers of the stylopharyngeus muscle spread between the constrictor muscles and the mucous membrane (blending to some extent with the constrictors) and pass caudally in the posterolateral wall of the pharynx, until they fade out and attach to the fibrous aponeurosis of the pharynx a short distance above the cricopharyngeus muscle. The stylopharyngeus muscle receives its nerve supply from the glossopharyngeal nerve, which curves around the posterior border of the muscle onto the lateral aspect in its course toward its final distribution on the posterior third of the tongue.

The *salpingopharyngeus muscle* consists of a slender bundle that produces the mucous membrane fold of the same name, which is rather variable in its degree of distinctness. This muscle arises from the inferior part of the cartilaginous part of the auditory tube, near its orifice, and passes into the wall of the pharynx, blending in part with the posteromedial border of the palatopharyngeus muscle. Some authors have described this muscle as a part of the *levator veli palatini muscle*, which gives a definite clue as to its action. The salpingopharyngeus muscle receives its nerve supply from the pharyngeal plexus.

The *palatopharyngeus muscle*, together with the mucous membrane covering it, forms the palatopharyngeal fold, also known as the posterior pillar of the fauces. This muscle takes its inferior origin from a narrow fasciculus on the dorsal border of the thyroid cartilage near the base of the superior horn and by a broad expansion from the *pharyngeal aponeurosis* in the area posterior to the larynx, just cranial to the cricopharyngeus muscle. As the fibers pass cranially, they form



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a rather compact muscular band that inserts into the aponeurosis of the soft palate by two lamellae, separated by the insertion of the levator veli palatini and the uvula. As indicated above, some of the fibers of the palatopharyngeus muscle intermingle with the stylopharyngeus muscle. The actions of the palatopharyngeus muscle include constriction of the pharyngeal isthmus by approximation of the palatopharyngeal folds, depression of the soft palate, and elevation of the

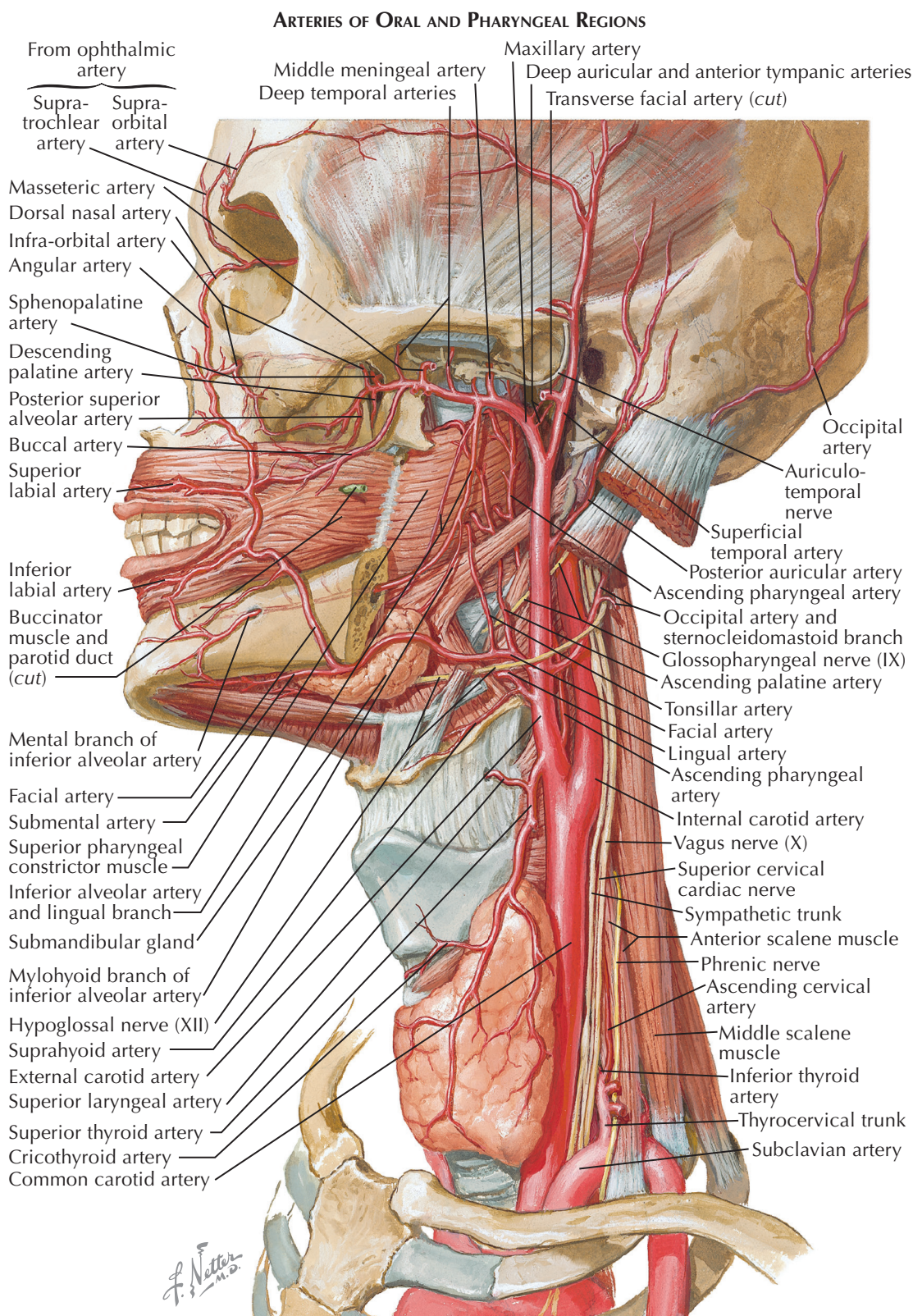
pharynx and larynx. This muscle also receives its nerve supply from the pharyngeal plexus.

Additional muscle bundles are quite common, such as the one labeled *accessory muscle bundle from petrous part of temporal bone (petropharyngeus muscle)*. Other additional muscles are brought about by the splitting of one of the usual muscles, quite commonly the stylopharyngeus. The majority of the additional muscles tend to run longitudinally.

BLOOD SUPPLY OF MOUTH AND PHARYNX

The *external carotid artery* and its branches are responsible for essentially the total arterial supply of the mouth and pharynx. The common carotid artery, arising from the brachiocephalic trunk on the right and the arch of the aorta on the left, bifurcates at the level of the superior border of the thyroid cartilage into external and internal carotid arteries. From here the external carotid artery courses superiorly to a point posterior to the neck of the mandible, dividing in the substance of the parotid gland into the *maxillary* and *superficial temporal arteries*. The parotid gland surrounds part of the external carotid artery and the beginnings of its terminal branches. The gland gets many small branches from these vessels in its substance.

Five of the branches of the external carotid artery are involved in the supply of the mouth and pharynx. The *superior thyroid artery* leaves the anterior aspect of the external carotid near its beginning and courses inferiorly and anteriorly on the external surface of the inferior pharyngeal constrictor muscle, passing deep to the sternohyoid and omohyoid muscles to ramify on the anterolateral surface of the thyroid gland. Near its origin, the *superior laryngeal artery* pierces the thyrohyoid membrane to supply the tissues of the larynx. The *lingual artery* arises from the anterior surface of the external carotid, a short distance superior to the superior thyroid artery, opposite the tip of the greater horn of the hyoid bone. It courses anteriorly and slightly superiorly deep to the stylohyoid muscle, the posterior belly of the digastric muscle, and the hypoglossal nerve, and then passes medial to the hyoglossus muscle along the superior border of the greater horn of the hyoid. The *facial artery*, coming from the anterior aspect of the external carotid slightly superior to the lingual, is tortuous throughout its length to allow for movements of the head and of the lower jaw. It courses anteriorly and superiorly deep to the digastric and stylohyoid muscles sheltered by the mandible, lies in a groove on the submandibular gland, and then curves superiorly around the inferior border of the mandible near the anterior margin of the masseter muscle. From here it runs anteriorly and superiorly across the cheek and along the side of the nose, to end as the *angular artery* at the medial angle of the eye. The *maxillary artery*, the larger of the two terminal branches of the external carotid, passes anteriorly between the ramus of the mandible and the sphenomandibular ligament (first part), and continues anteriorly either deep or superficial to the lateral pterygoid muscle (second part), between the two heads of which it dips to reach the pterygopalatine fossa (third part). The *infraorbital artery*, which is a continuation of the maxillary, courses through the infraorbital canal of the maxilla to end in terminal branches on the face as it leaves the infraorbital foramen. The *ascending pharyngeal artery* arises from the posteromedial aspect of the external carotid very near its beginning. From here it ascends vertically between the internal carotid artery and the posterolateral aspect of the pharynx, to go as high as the undersurface of the base of the skull.



The lips, which are very vascular, are supplied chiefly by the *superior* and *inferior labial* branches of the facial artery, each of which courses from near the angle of the mouth, where they arise, toward the midline of each respective lip to meet the one on the opposite side. For the most part, they lie between the orbicularis oris muscle and the mucous membrane related to its inner surface. The *mental branch of the inferior alveolar artery*, a branch of the first part of the maxillary artery,

anastomoses with the inferior labial artery, and the labial branch of the *infraorbital artery* anastomoses with the superior labial artery.

The cheek receives much of its arterial supply by way of the *buccal artery*, which springs from the second part of the maxillary artery and runs anteroinferiorly on the external surface of the buccinator muscle.

The arterial supply of the superior arcade of teeth, their alveolar processes, and gums is furnished in the

BLOOD SUPPLY OF MOUTH AND PHARYNX (Continued)

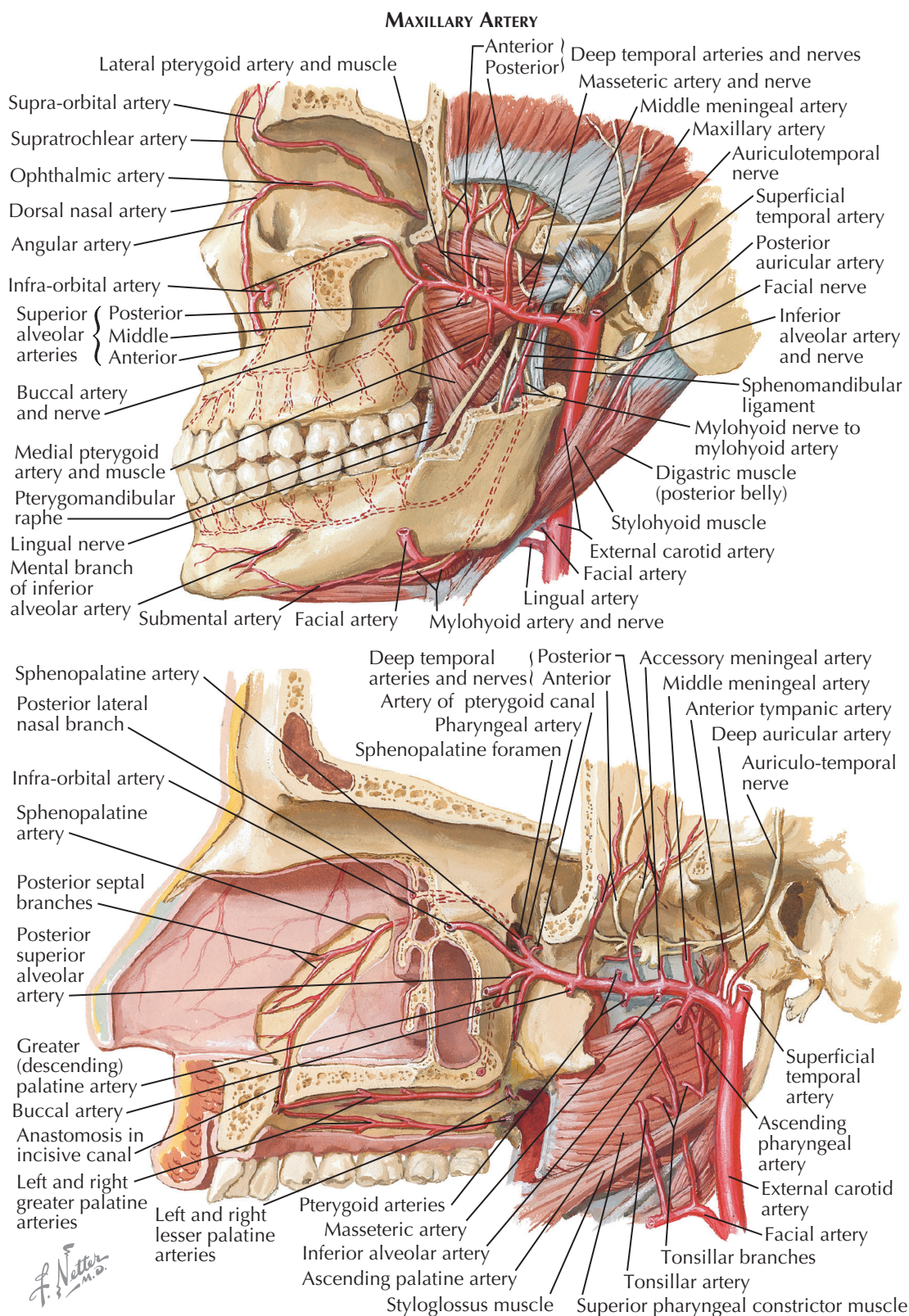
molar and premolar area by the *posterior superior alveolar artery*, which arises from the second part of the maxillary artery. It courses inferiorly in the pterygopalatine fossa to divide into several small branches, most of which enter small foramina on the posterior aspect of the maxilla. The *anterior* and less constant *middle superior alveolar branches* of the infraorbital artery pass along the wall of the maxillary sinus to supply the rest of the upper jaw.

The inferior arcade of the teeth with the related bone and gums are supplied by the *inferior alveolar artery*. It enters the mandibular foramen to course in the alveolar canal and ends as the *mental artery*, which gives off an incisive branch before exiting through the mental foramen to supply the chin.

The arterial supply of the tongue is, for the most part, by way of the lingual artery. The anastomoses between the branches of the right and left lingual arteries are of a small enough caliber so that ligation of one artery makes that side of the tongue sufficiently bloodless for an operative procedure. Under cover of the posterior border of the hyoglossus muscle, the lingual artery gives off *dorsal lingual branches*, which travel superiorly and medial to the styloglossus muscle to supply the mucous membrane of the dorsum as far back as the epiglottis, anastomosing with other vessels supplying the tonsil. The portion of the artery from the anterior border of the hyoglossus forward to the tip of the tongue is the *deep lingual artery*, which lies deep to the genioglossus muscle and is under cover of the mucous membrane on the inferior surface of the tongue.

The mucous membrane of the floor of the mouth and the sublingual gland receive blood through the sublingual artery, which branches from the lingual near the anterior border of the hyoglossus muscle and courses anterior and superior to the mylohyoid muscle and lateral to the genioglossus. The muscles of the floor of the mouth are supplied by the submental branch of the facial artery and the mylohyoid branch coming off from the inferior alveolar just before it enters the mandibular foramen. These two arteries contribute some blood to the submandibular gland, which gets most of its supply from the nearby facial artery.

The arterial supply of the palate is chiefly from the *descending palatine branch* of the third part of the maxillary artery, which travels inferiorly through the *pterygopalatine canal* to emerge from the greater palatine foramen and then courses anterior, medial to the alveolar process, to anastomose at the incisive foramen with a septal branch of the *sphenopalatine artery*. The *lesser palatine artery*, which runs posteriorly from the descending palatine at the greater palatine foramen, supplies the soft palate and anastomoses with other arteries that supply the tonsil. Anastomoses exist also with a palatine branch of the ascending pharyngeal artery, the dorsal lingual arteries, and the ascending palatine from the facial artery.



The muscles of mastication receive arterial twigs, named according to the muscle supplied, from the second part of the maxillary artery.

The pharynx receives blood from many sources, the amount from each source varying a great deal individually. One of the chief sources is the *ascending pharyngeal artery*, usually from the external carotid artery. Other arteries that run to the pharynx and can thus contribute to its supply are the ascending palatine and tonsillar

branches of the facial artery, the superior thyroid artery and its superior laryngeal branch, and the inferior laryngeal and ascending cervical branches of the thyrocervical trunk from the subclavian artery. The pharyngeal branch of the third part of the facial artery passes through a bony canal to reach the roof of the pharynx, and the descending palatine artery, also from the third part of the facial, contributes to the supply in the region of the tonsil by its lesser palatine branches.

VENOUS DRAINAGE OF MOUTH AND PHARYNX

As elsewhere in the body, the veins of the face, oral cavity, and pharynx are more variable than are the arteries. The veins in this region tend to lie more superficially than the arteries and form plexuses substituting for single, definite vessels.

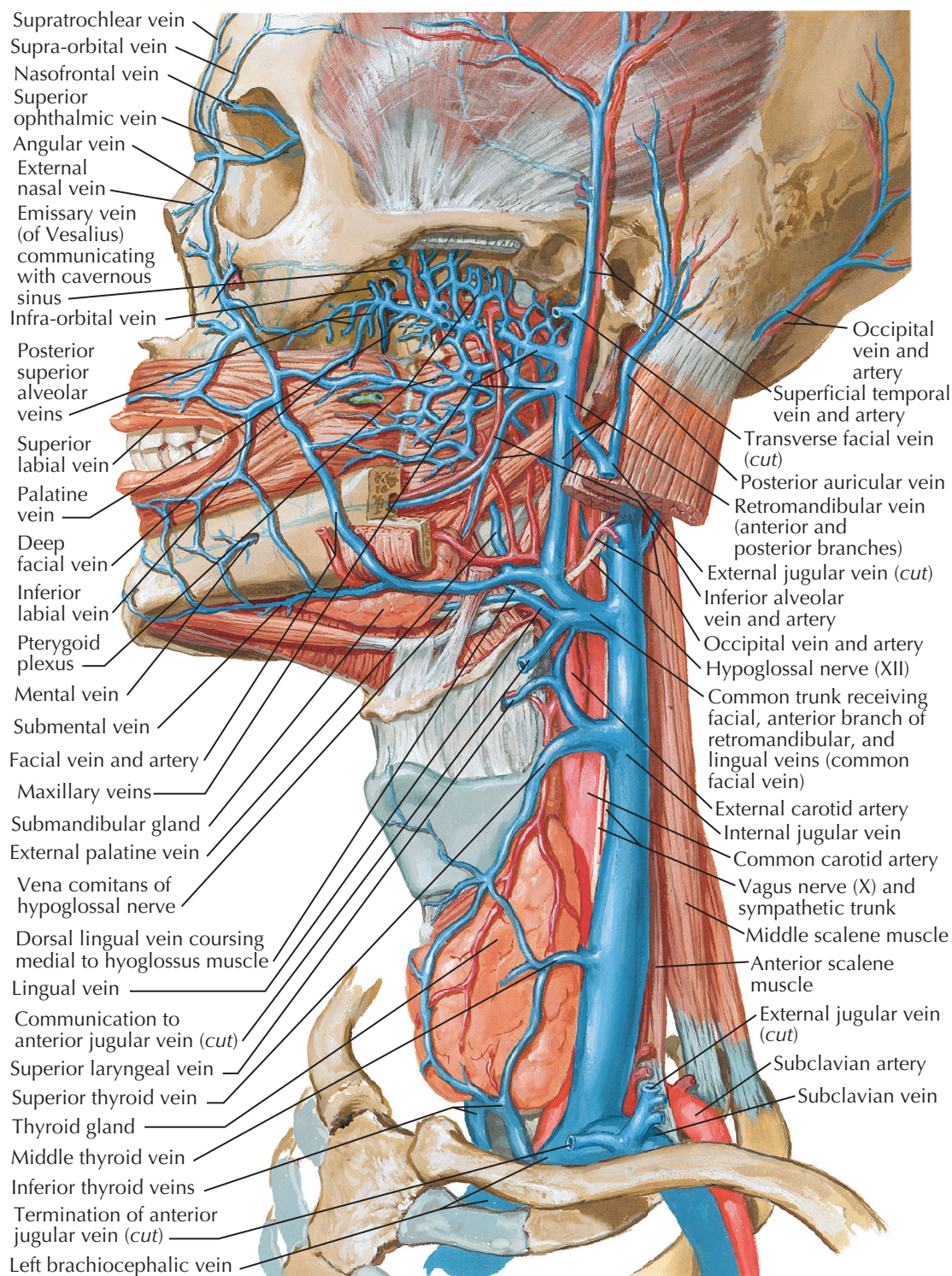
The *internal jugular vein* eventually receives almost all of the blood derived from the mouth and pharynx. This vein begins as a continuation of the *sigmoid sinus* at the *jugular foramen* and descends in the neck lateral to the *internal* and then *common carotid arteries* to about the level of the *sternoclavicular joint*, where it joins the *subclavian vein* to form the *brachiocephalic vein*.

For the most part, the arteries described in the previous section have veins of the same name accompanying them, but the veins into which these drain differ in various ways from the branches of the external carotid artery. The *superior thyroid vein* does not differ greatly from the superior thyroid artery, but it does usually empty directly into the internal jugular vein. Frequently, one encounters a *middle thyroid vein* with no corresponding artery that also empties into the internal jugular vein.

The *deep lingual vein*, often more than one channel, accompanies the corresponding artery from the tip of the tongue to the anterior border of the hyoglossus muscle, where the major vein receives the sublingual vein and then accompanies the hypoglossal nerve on the lateral surface of the hyoglossus muscle, as well as a smaller vein(s) that runs alongside the lingual artery. Near the posterior border of the hyoglossus muscle, one of these veins receives the *dorsal lingual veins*, and then they either join to form a short *lingual vein* or continue separately to empty either into the *common facial vein* or directly into the *internal jugular vein*.

The *facial vein* follows a not-so-tortuous path (compared with the artery) from the medial angle of the eye to the lower border of the mandible near the anterior margin of the masseter muscle. From here it courses posteriorly in the submandibular triangle (not as sheltered by the mandible as the artery) to join the anterior division of the *retromandibular vein* in the formation of a *common trunk* that empties into the internal jugular vein. The anterior facial vein receives tributaries corresponding mostly to the branches of the facial artery but also some communications from the *pterygoid plexus*, one of which is often called the deep facial or external palatine vein.

The *maxillary vein* is sometimes a distinct vein with tributaries corresponding to the artery, but more commonly appears as one or more short veins that drain the *pterygoid plexus* and join the *superficial temporal vein* in the formation of the *retromandibular vein*. The pterygoid plexus is partly superficial and partly deep to the



lateral pterygoid muscle. The tributaries are those veins that correspond to the branches of the *maxillary artery*, and the plexus communicates with the *cavernous sinus* by small veins passing through the foramina in the floor of the middle cranial fossa and with the pharyngeal plexus, in addition to the other connections previously mentioned.

The bulk of a pharyngeal plexus of veins lies superficial to the pharyngeal constrictor muscles. This plexus communicates in all directions, with connections to the

internal and external jugular veins, pterygoid plexus, common facial vein, lingual vein, superior thyroid vein, and a submucosal plexus, which is best developed in the lower part of the posterior pharyngeal wall.

The posterior division of the retromandibular vein joins the *posterior auricular vein* to form the *external jugular vein*, and an *anterior jugular vein* begins in the chin superficial to the mylohyoid muscle and courses inferiorly and then laterally to empty into the external jugular vein.

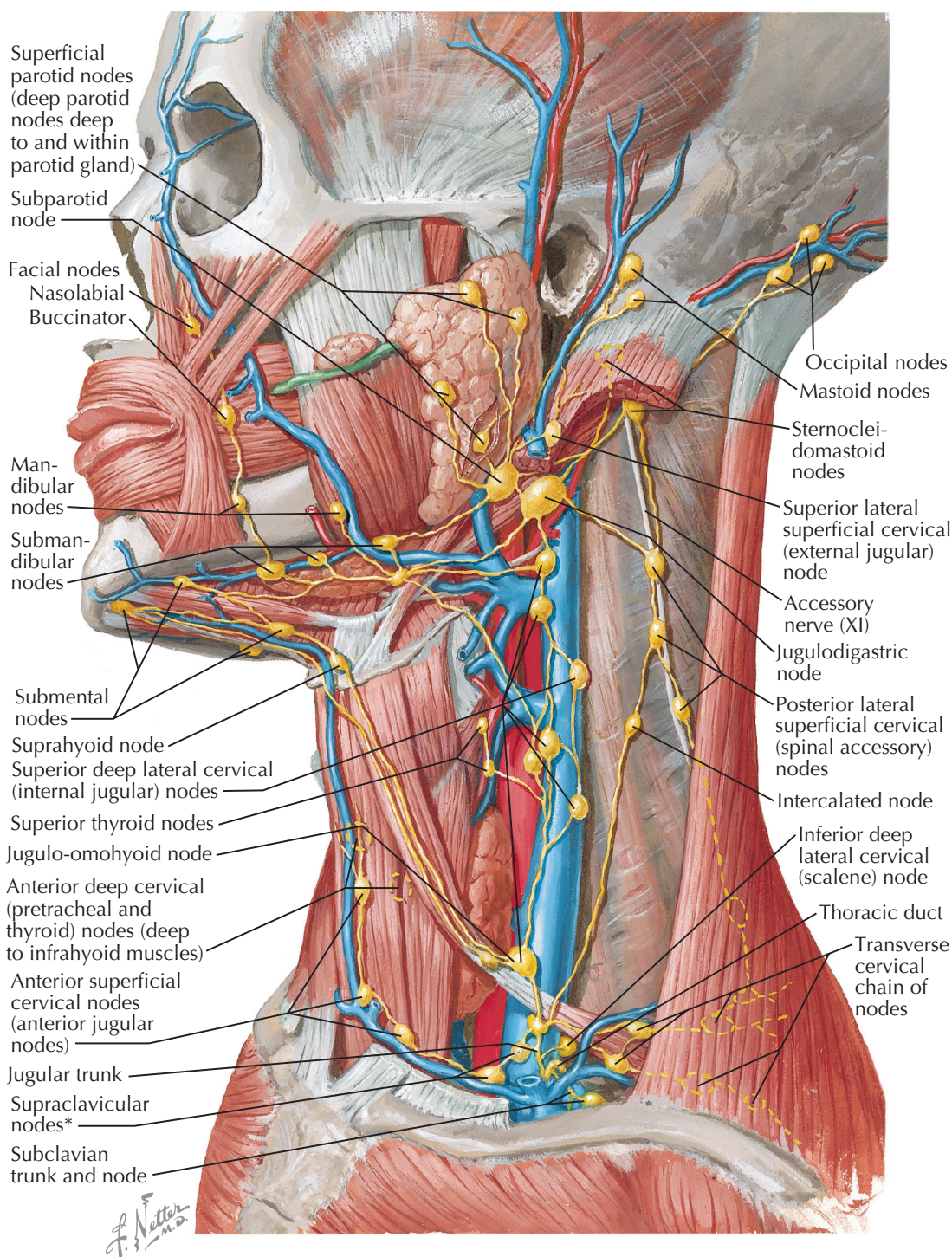
LYMPH VESSELS AND NODES OF HEAD AND NECK

LYMPHATIC DRAINAGE OF MOUTH AND PHARYNX

Lymphatic fluid, carried by the lymphatic capillaries in the tissues of the mouth and pharynx, is all eventually taken by the lymphatic vessels, either directly or with the interruption by interposed lymph nodes, to the *chain of lymph nodes* lying along the *internal jugular vein*. The efferent vessels from these nodes enter into the formation of the *jugular lymphatic trunk*, which, characteristically, on the left side empties into the *thoracic duct* near its termination and on the right side into the *right lymphatic duct*. The thoracic duct and the right lymphatic duct pour their lymph into the bloodstream at the junction of the *internal jugular* and *subclavian veins* on the respective side. On either side the jugular trunk may empty directly into the veins near this site.

A more specific description of the lymph nodes involved in the lymphatic drainage of the mouth and pharynx is necessary because of their importance in the metastasis of cancer and the significance attached to the enlargement of a node when an infection occurs in its area of drainage. However, any specific description of lymph nodes is complicated by the facts that lymphatics are quite variable and are difficult or impossible to see in dissection when they are not pathologically conspicuous and that the grouping of the nodes is at best arbitrary and, to quite an extent, artificial. Because of this, descriptions of lymphatics vary greatly, and many different names have been employed for individual nodes and groups of nodes. The number of groups of nodes described for any region can, of course, differ, depending on whether certain nodes are interpreted as forming a separate group or are considered as subsidiaries of another group.

The grouping of the nodes of the head and neck can be described briefly as follows: A *pericervical collar* of nodes is located at the general region of the junction of the head and neck. From the midline posteriorly to the midline anteriorly, the groups encountered, in order, are *occipital*, *mastoid*, *parotid*, *submandibular*, and *submental* nodes. A group of nodes superficial to the sternocleidomastoid muscle and in close relation to the external jugular vein is called the *superficial cervical group* of nodes; however, some consider them to be an extension of the parotid group. The majority of the groups of nodes not included in the "collar" just described run more or less vertically in the neck. Minor chains of nodes lie along the *anterior jugular vein* and the *spinal accessory nerve*, and a major chain of nodes accompanies the internal jugular vein along its entire length. The latter is most commonly designated as the *deep cervical group* of nodes and is often divided into *superior deep cervical nodes* superior to the point at which the omohyoid muscle crosses the internal jugular vein and the *inferior deep cervical nodes* inferior to this point. The



*The supraclavicular group of nodes (also known as the lower deep cervical group), especially on the left, are also sometimes referred to as the *signal* or *sentinel lymph nodes* of Virchow or Troisier, especially when sufficiently enlarged and palpable. These nodes (or a single node) are so termed because they may be the first recognized presumptive evidence of malignant disease in the viscera.

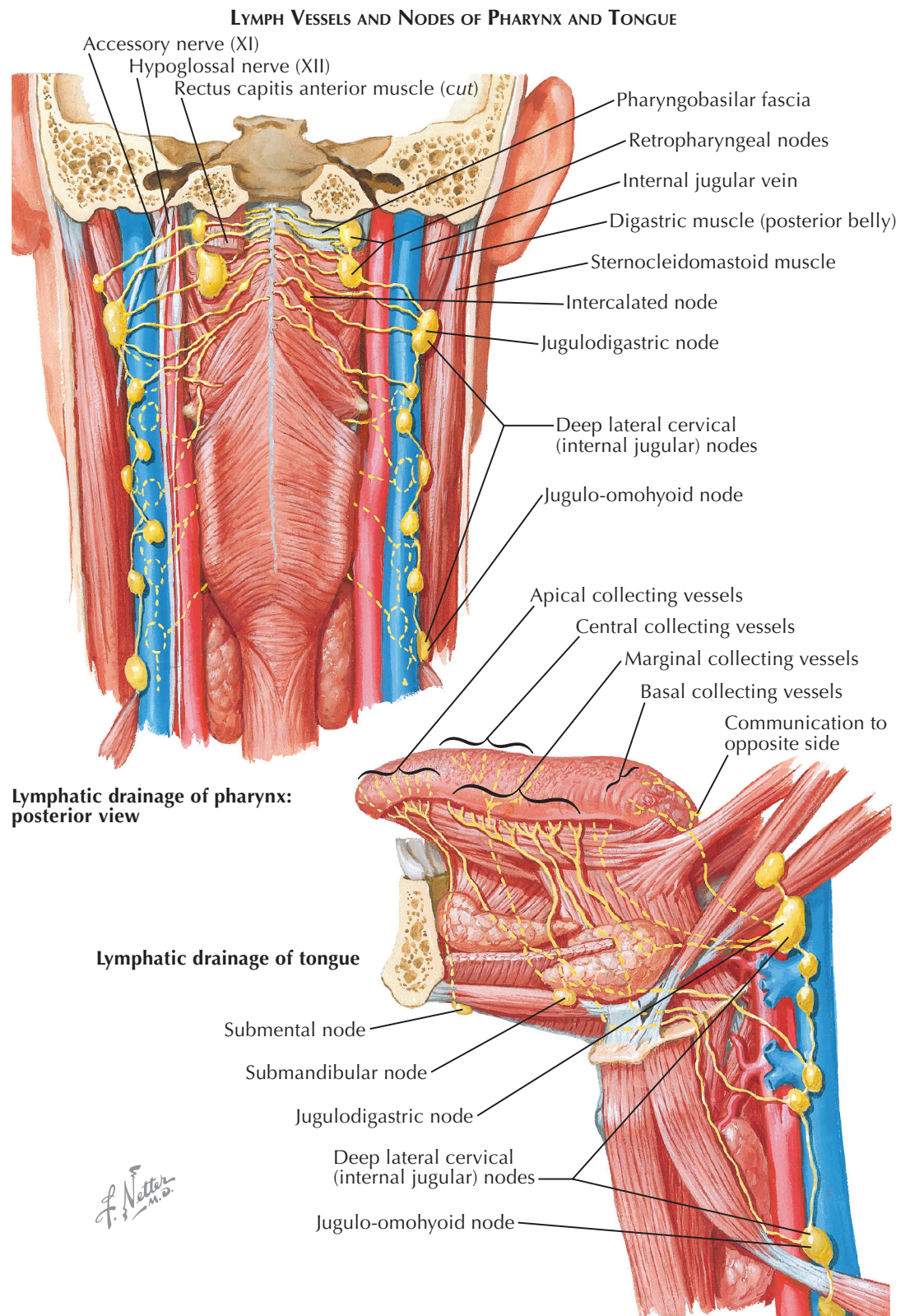
retropharyngeal nodes may be an expansion of the superior portion of the superior deep cervical group or a separate group of nodes located between the superolateral part of the pharynx and the prevertebral fascia. Individual nodes are encountered constantly enough in two locations in the superior deep cervical chain that they have merited special naming. A *jugulodigastric node* is located between the angle of the mandible and the anterior border of the sternocleidomastoid muscle, at about the level of the greater horn of the hyoid bone

and between the posterior belly of the digastric muscle and the internal jugular vein. This node receives lymph from the area of the palatine tonsil, tongue, and teeth. A *juguloomohyoid node*, usually considered as the lowest node of the superior deep cervical group, lies immediately superior to the intermediate tendon or the inferior belly of the omohyoid muscle and may project beyond the posterior border of the sternocleidomastoid muscle. This node receives some vessels directly from the tongue in addition to its other afferents. A *subparotid*

LYMPHATIC DRAINAGE OF MOUTH AND PHARYNX (Continued)

node just inferior to the parotid gland is specially named by some authors. The inferior deep cervical nodes, also called *supraclavicular nodes*, extend into the posterior triangle of the neck, send expansions along the transverse cervical and transverse scapular veins, and intermingle with the *subclavian* and *apical axillary lymph nodes*. In addition to the groups of nodes described above, some scattered nodes, part of which are often called *anterior deep cervical nodes*, pertain to the larynx, trachea, esophagus, and thyroid gland.

The groups of nodes specifically involved in the drainage of lymph from specific portions of the mouth and pharynx are indicated briefly in the following statements: The **LIPS** have cutaneous and mucosal plexuses from which the lymph drains to the submandibular, submental, and (to a slight extent) superficial cervical groups. Lymph from the **CHEEK** travels mostly to the submandibular nodes but also to superficial cervical nodes and, in part, directly to superior deep cervical nodes. From the anterior part of the **FLOOR OF THE MOUTH**, drainage is, in part, directly to the lower of the superior deep cervical group and, in part, to the submental and submandibular nodes. The posterior part drains to submandibular and superior deep cervical nodes. Lymph from the **HARD and SOFT PALATES** may travel directly to superior deep cervical nodes (near the digastric muscle) or to submandibular nodes or, particularly from the soft palate, to retropharyngeal nodes. The lymphatics of the **TEETH** anastomose with those of the **GUMS**. Lymph from the superomedial alveolar processes drains similarly to the palate, whereas lymph from the inferomedial alveolar processes drains similarly to the floor of the mouth. Drainage from the lateral alveolar processes is similar to that of the lips and cheek. The jugulodigastric node, or at least a node in that area, may be enlarged when a tooth, particularly in the molar region, is infected. The lymphatic drainage of the **TONGUE** goes either directly or indirectly to the superior deep cervical nodes, and, in general, the farther forward the area on the tongue, the lower in the deep cervical chain is the related node. Four sets of collecting vessels of the tongue are described: *apical vessels* lead to submental nodes and the jugulo-omohyoid node; *marginal vessels* to superior deep cervical nodes and perhaps submandibular nodes; *basal vessels* to superior deep cervical nodes (chiefly, the jugulodigastric node); and *central vessels* mostly to superior deep cervical nodes, with a few to submandibular nodes. The central vessels from each side of the tongue go to



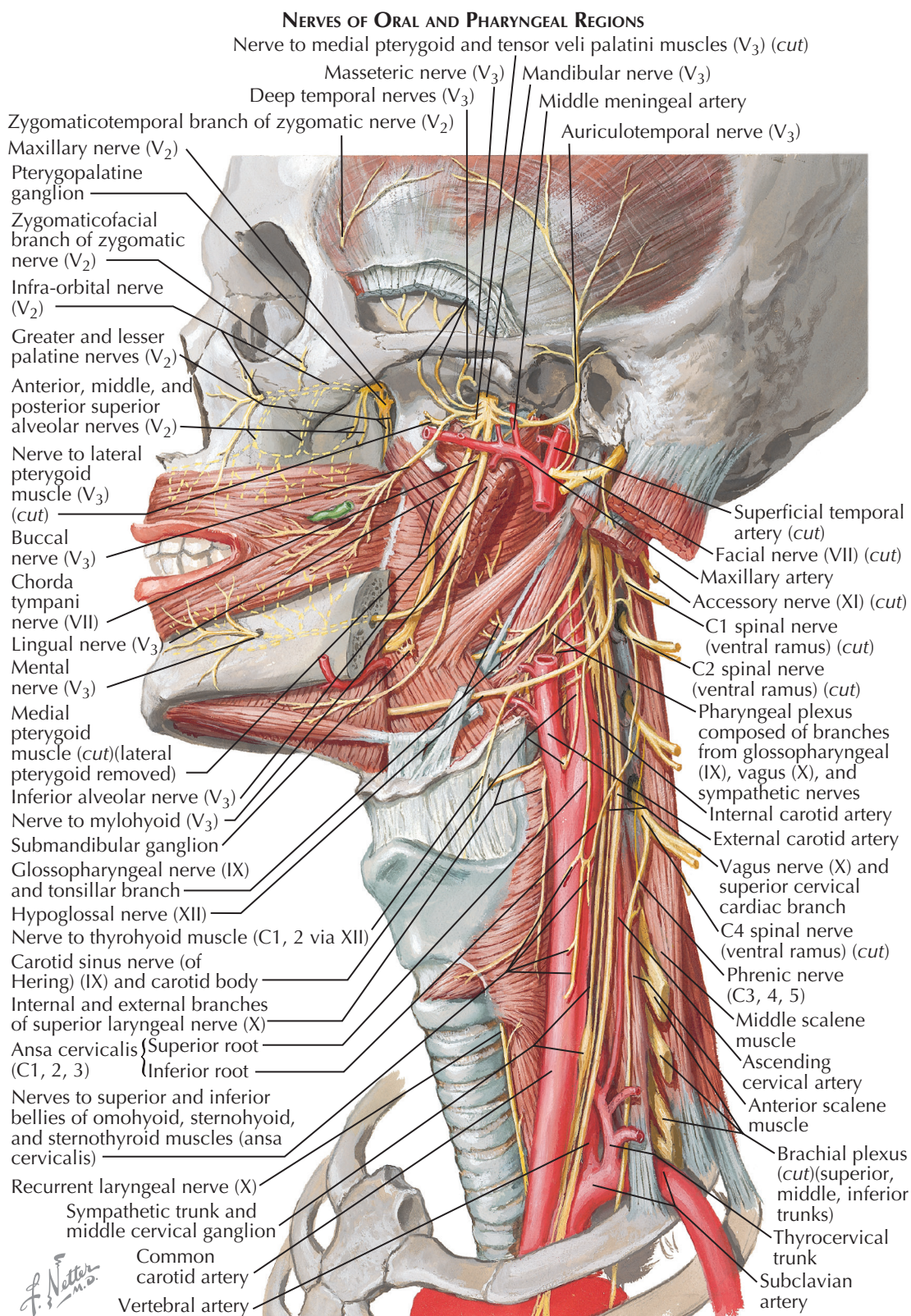
both right and left superior deep cervical nodes. No vessels from the tongue are said to reach any of the more superficial nodes. Drainage from the **LARGE SALIVARY GLANDS** is much as would be expected: parotid gland to parotid nodes (some of which are described as being in the substance of the gland); submandibular gland, in part to submandibular nodes but mostly to superior deep cervical nodes; and sublingual gland, much like that of the submandibular gland. Part of the

lymph from the area of the **PALATINE TONSIL** goes to the superior deep cervical nodes and much of it to the jugulodigastric node. The mucosa of the **PHARYNX** is rich in lymphatics, and the drainage from the roof and upper part of the posterior wall is to the retropharyngeal nodes. The collecting vessels of the laryngeal pharynx gather in the wall of the piriform sinus, pierce the thyrohyoid membrane, and continue to nearby superior deep cervical nodes.

NERVE SUPPLY OF MOUTH AND PHARYNX

Six of the 12 pairs of cranial nerves contribute to the nerve supply of the mouth and pharynx. The *trigeminal nerve* (cranial nerve V) emerges from the lateral surface of the pons as a larger sensory and a smaller motor root. A short distance from the pons the sensory root is expanded by the presence of many afferent nerve cell bodies into the *trigeminal ganglion*, which lies in a depression on the apex of the petrous portion of the temporal bone. From the anterior margin of this ganglion arise the ophthalmic, maxillary, and mandibular divisions of the trigeminal nerve. The motor root courses along the medial and then the inferior side of the sensory root and ganglion and joins the *mandibular nerve* near its beginning. The *maxillary division* passes through the foramen rotundum into the pterygopalatine fossa, where it gives off the following branches: (1) two or three branches to the *sphenopalatine ganglion*, which leave the ganglion as a pharyngeal branch passing through a bony canal to the mucous membrane of the upper part of the nasopharynx, the *palatine nerves* passing through the pterygopalatine canal to exit through the greater and lesser palatine foramina to supply the mucous membrane of the palate, and a sphenopalatine branch, which enters the nasal cavity and runs along the nasal septum to reach the palate through the incisive foramen; (2) the *posterior superior alveolar nerves*, which enter the maxilla and supply the molar teeth and related gums. The maxillary nerve continues as the *infraorbital nerve*, which gives off the *middle* and *anterior superior alveolar nerves* in the infraorbital canal and a branch to the upper lip after it reaches the face. The mandibular nerve reaches the infratemporal fossa through the foramen ovale and has the following branches: (1) nerves to each of the muscles of mastication (the nerve to the *medial pterygoid* also supplying the *tensor veli palatini muscle*); (2) the inferior alveolar, which, before entering the mandibular foramen, gives off the *mylohyoid branch* to that muscle and the anterior belly of the digastric, courses through the alveolar canal supplying the mandibular teeth, and ends as the *mental nerve*, which exits through the mental foramen to give sensory supply to the chin and part of the lower lip; (3) the *buccal nerve* giving sensory supply to the cheek; and (4) the *lingual nerve*, which, after receiving the chorda tympani from the facial nerve, courses inferiorly and then anteriorly on the lateral surface of the hyoglossus muscle to reach the undersurface of the tongue. The trigeminal fibers in the lingual nerve carry general sensation from the anterior two thirds of the tongue.

The *facial nerve* (cranial nerve VII) emerges from the lateral side of the pontomedullary junction as a larger motor and a smaller sensory root (nervus intermedius), containing general visceral efferent fibers of VII as well as afferent fibers. It leaves the cranial cavity by way of



the internal acoustic meatus and then goes through the *facial canal* to exit the stylomastoid foramen, where it gives off branches to the stylohyoid muscle and posterior belly of the digastric. The facial nerve runs anteriorly through the substance of the parotid gland, crosses the external carotid artery, and divides in the substance of the gland into branches that leave the anterior border of the parotid gland to innervate the muscles of facial expression, of which the ones surrounding the oral orifice, including the buccinator, are of interest in this

discussion. The *geniculate ganglion* is present within the facial canal at a sharp bend in the nerve. Proximal to the ganglion, the nerve gives off the *greater petrosal nerve*, which eventually reaches the pterygopalatine ganglion. Distal to the ganglion it gives off the *chorda tympani*, which eventually joins the lingual nerve, carrying special visceral afferent fibers, which carry taste sensation from the anterior two thirds of the tongue, as well as preganglionic parasympathetic axons, which go to the *submandibular ganglion*.

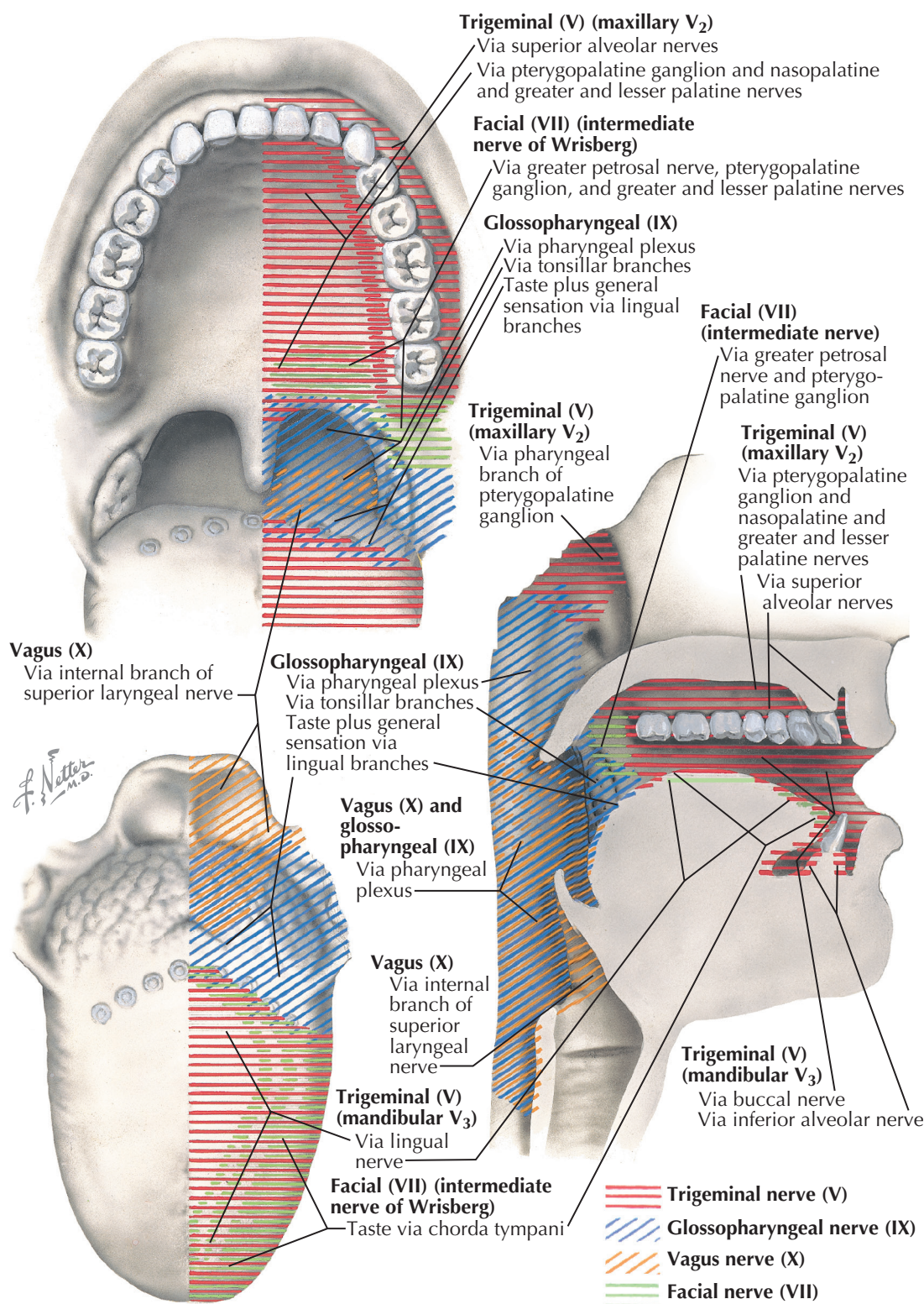
NERVE SUPPLY OF MOUTH AND PHARYNX (Continued)

The *glossopharyngeal nerve* (cranial nerve IX) emerges by a series of rootlets from the cranial part of the groove between the inferior cerebellar peduncle and the inferior olive of the medulla. It leaves the cranial cavity through the jugular foramen near which it exhibits two ganglionic swellings, courses downward along the posterior border of the stylopharyngeus muscle, and disappears deep to the hyoglossus muscle to ramify into its terminal branches to the tongue. The tympanic branch of the glossopharyngeal nerve follows a bony canal from the margin of the jugular foramen to the tympanic cavity, where it helps to form the tympanic plexus and then continues as the *lesser petrosal nerve*, which eventually brings preganglionic parasympathetic axons to the *otic ganglion*. The pharyngeal branches of the glossopharyngeal nerve mostly join with the pharyngeal branches of the vagus and branches of the superior cervical ganglion to form the pharyngeal plexus, which supplies the muscles of the pharynx (except the stylopharyngeus, entirely glossopharyngeal) and the muscles of the soft palate (except the tensor veli palatini, mandibular branch of trigeminal). The pharyngeal plexus consists of motor axons from the vagus and sensory axons to the mucous membrane via the glossopharyngeal, except for a muscular branch of the glossopharyngeal that innervates the stylopharyngeus muscle. The *tonsillar branches* arise near the base of the tongue and supply also the soft palate and the fauces. The *lingual* and *terminal branches* of IX take care of both the general sense and the sense of taste of the posterior one third of the tongue and the pharyngoepiglottic folds.

The *vagus nerve* (cranial nerve X) emerges just inferior to the glossopharyngeal nerve. It also leaves the cranial cavity by way of the jugular foramen and has two ganglionic swellings in this region, one at the foramen and one below the foramen. Entering the carotid sheath, the vagus courses inferiorly in the neck between the internal jugular vein and the internal or common carotid artery. Some branches of the vagus contribute to the supply of the mouth and pharynx. The *pharyngeal branches* (variable in number) supply motor axons to the pharyngeal plexus. The *superior laryngeal nerve* divides into external and internal branches. The external branch runs inferiorly and anteriorly on the external surface of the inferior pharyngeal constrictor to innervate the cricothyroid and cricopharyngeus muscles and a variable amount of the inferior pharyngeal constrictor. The internal branch pierces the thyrohyoid membrane and divides into an ascending and a descending branch, the former going to the mucous membrane covering the epiglottis and a small adjacent part of the tongue and the latter supplying the mucous membrane on the pharyngeal surface of the larynx in addition to its laryngeal distribution. The recurrent laryngeal branch of the vagus gives some supply to the inferior pharyngeal constrictor muscle as the branch passes under the inferior border of this muscle in entering the larynx.

The *hypoglossal nerve* (cranial XII) emerges by a series of rootlets from the sulcus between the inferior olive and the medullary pyramid. It leaves the cranial cavity

AFFERENT INNERVATION OF ORAL CAVITY AND PHARYNX



by way of the hypoglossal canal and runs inferiorly and anteriorly, passing lateral to the carotid bifurcation and between the internal carotid artery and the internal jugular vein. It becomes superficial to the vessels near the angle of the mandible, where it passes across the external carotid and lingual arteries deep to the digastric muscles. From here it continues anteriorly between the mylohyoid and hyoglossus muscles. The hypoglossal nerve supplies the intrinsic muscles of the tongue,

as well as the styloglossus, hyoglossus, and genioglossus muscles. Fibers from the first and second cervical nerves run with the hypoglossal to supply the geniohyoid and thyrohyoid muscles.

The areas of sensory supply of the mucous membrane of the oral cavity and pharynx, shown diagrammatically in the accompanying illustration, are only approximations because no complete agreement as to their limits exists.

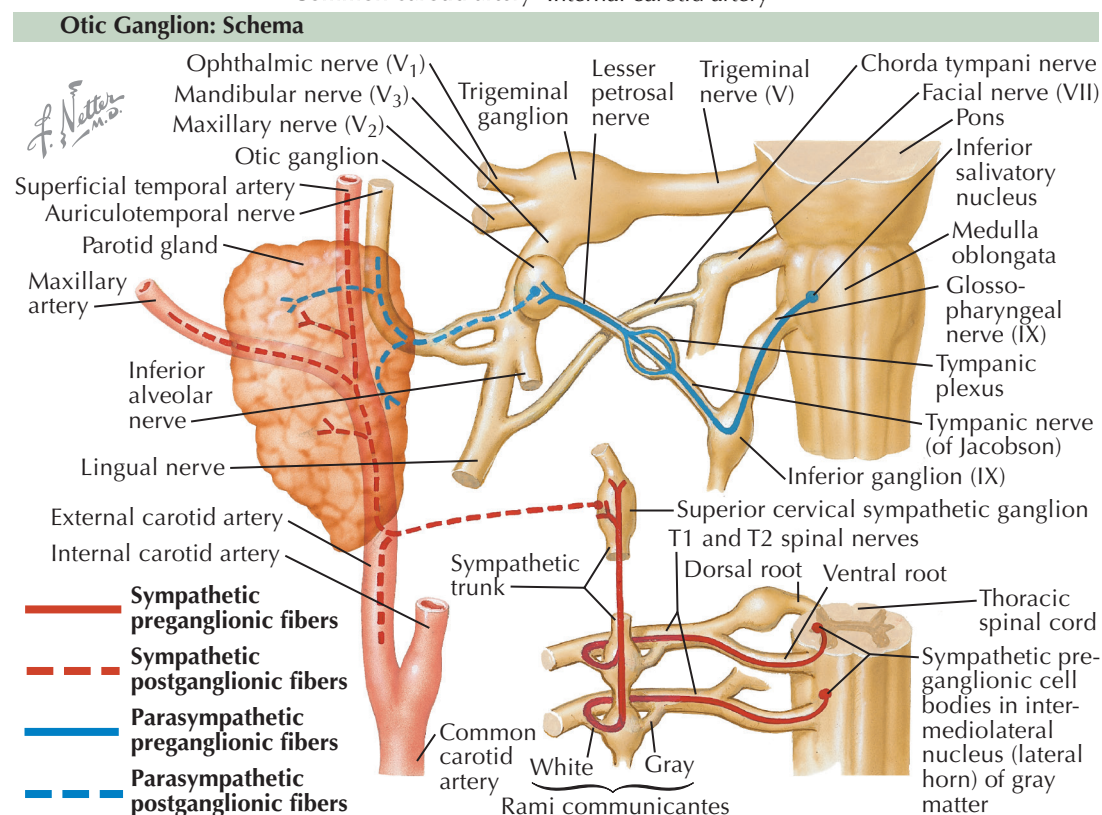
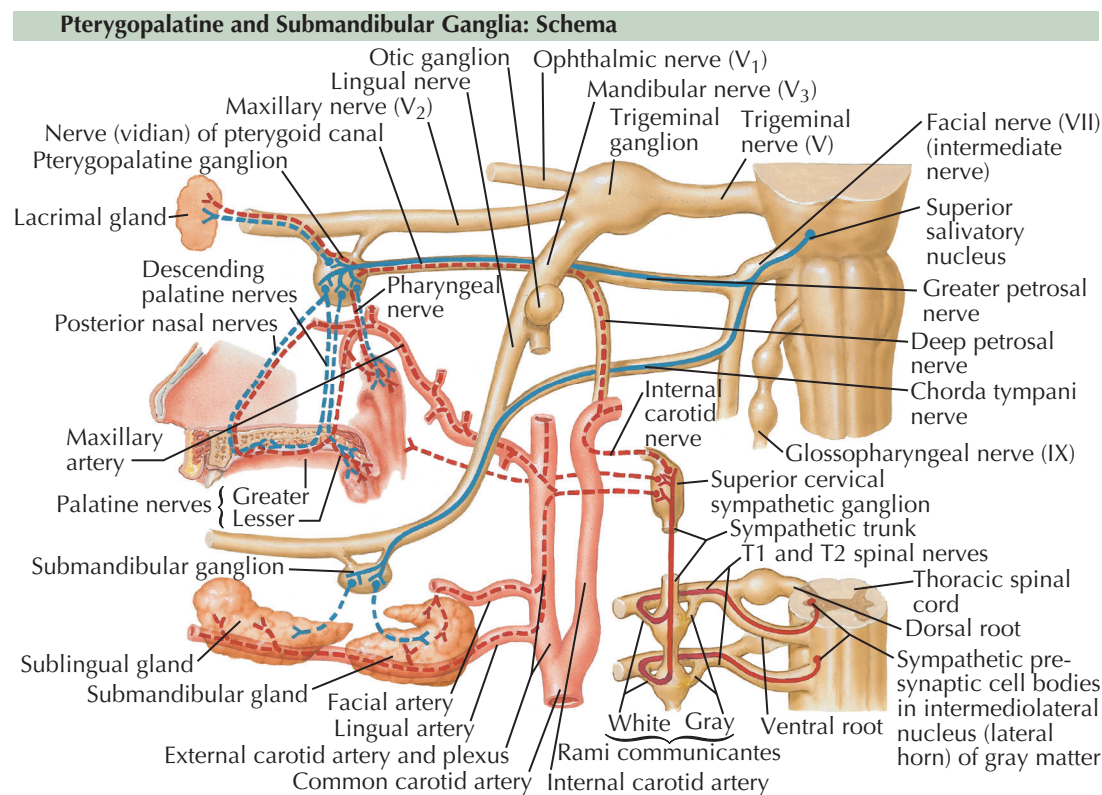
AUTONOMIC INNERVATION OF MOUTH AND PHARYNX

Autonomic (general visceral efferent) nerves innervate glands and the smooth muscle. The smooth muscle of the mouth and pharynx is largely found in the walls of blood vessels and erector pili muscles in the skin. Glands receive both sympathetic and parasympathetic axons that modulate their activity. Typically, this occurs via a two-neuron chain with the cell body of the first neuron in the central nervous system and the cell body of the second neuron in a peripheral ganglion.

For the palatine glands, the cell body of the first-order parasympathetic neuron is located in the superior salivatory nucleus of the pons, and the axon of this neuron follows the nervus intermedius root of VII, the greater petrosal nerve of VII, and then the *nerve of the pterygoid canal* (vidian nerve) to reach the *pterygopalatine ganglion*, where it synapses with the cell body of the second-order neuron. The axon of this second-order neuron follows the palatine nerves and their branches to be distributed along the palate. For sympathetic input to the palatine glands, the first-order neuron cell body is located in the intermediolateral cell column of the upper thoracic segments of the spinal cord. The axon of this neuron follows the anterior root of the related thoracic nerve, the spinal nerve, and the anterior primary ramus to the white ramus communicans, along which it passes to the sympathetic ganglion at that level. Thereafter the first-order axon ascends in the sympathetic trunk to synapse with the second-order neuron in the *superior cervical ganglion*. The axon of this second-order neuron enters the periarterial plexus of the nearby internal carotid artery and may take two courses. One follows the plexus superiorly to the carotid canal and then leaves the plexus as the deep petrosal nerve, which joins the greater petrosal nerve in the foramen lacerum to form the nerve of the pterygoid canal. The sympathetic fibers pass through the sphenopalatine ganglion without synapse and follow the palatine nerves to their distribution. The other course follows periarterial plexuses all the way to the distribution of the greater and lesser palatine arteries.

For the innervation of the submandibular and sublingual glands, the first-order parasympathetic neuron reaches the facial nerve, as described above for the innervation of the palatine glands, and then follows the *chorda tympani* branch to the lingual nerve. The axon then accompanies the lingual nerve until it leaves by a branch to the *submandibular ganglion*, where the pathway to the sublingual gland synapses. Many of the fibers carrying impulses to the submandibular gland itself pass through this ganglion to synapse in small ganglia on the surface of the gland. Axons of the second-order neurons go directly to the submandibular and sublingual glands. Those destined for the latter may follow the lingual nerve on their way. The sympathetic supply to these two glands follows the course described above for the palatine gland as far as the periarterial plexus. From there, axons follow arteries to the submandibular and sublingual glands.

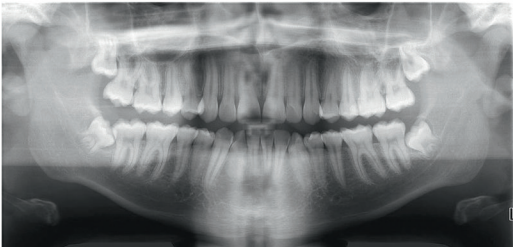
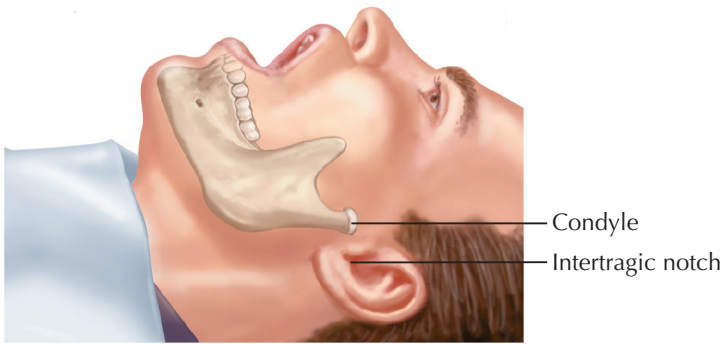
For the innervation of the parotid gland, the first-order parasympathetic neuron has its cell body in the inferior salivatory nucleus of the medulla, and the axon of this neuron follows the glossopharyngeal nerve, its *tympanic branch*, and then the *lesser petrosal nerve* to the



otic ganglion, where it synapses with the second-order neuron cell body. The axon of this neuron follows the *auriculotemporal nerve* to the parotid gland. The sympathetic innervation is similar to that described above for the submandibular and sublingual glands.

For the parasympathetic supply of small glands not discussed, one must assume that axons of second-order

neurons with cell bodies in the parasympathetic ganglia, described above, follow nerves going to the area, or that the parasympathetic fibers in VII, IX, or X synapse in small ganglia in the area. For the sympathetic supply, second-order neuron cell bodies in the superior cervical ganglion can send axons by any convenient nerve or periarterial plexus.

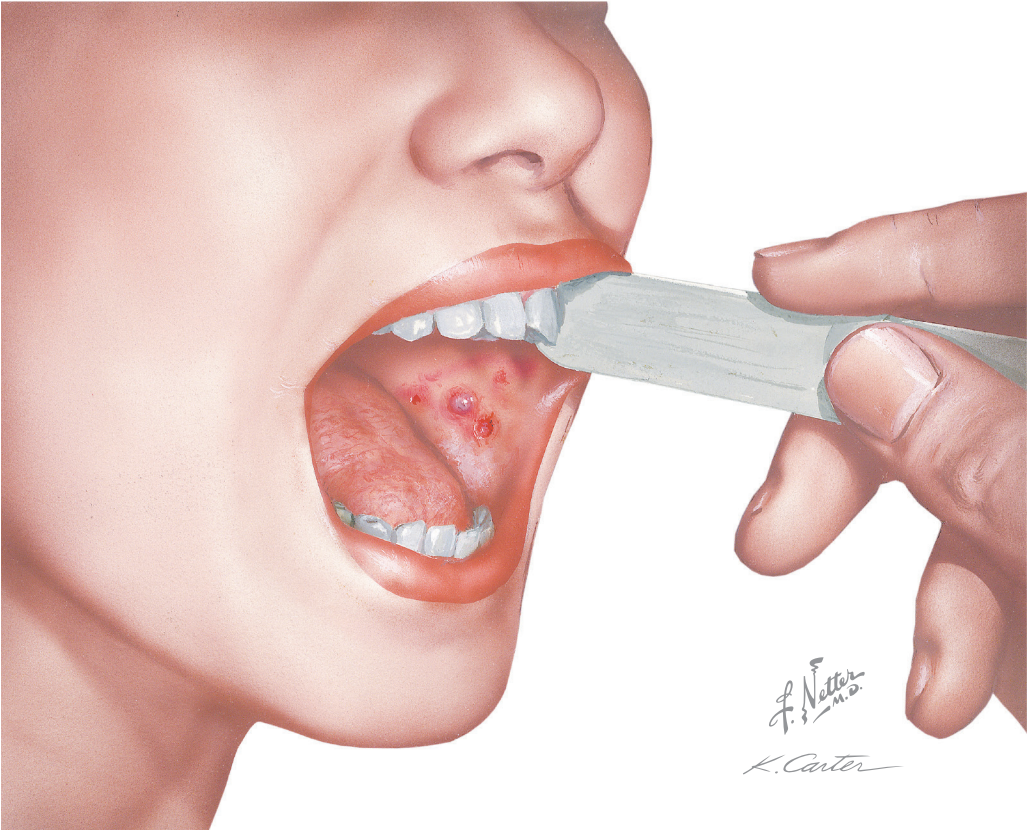


Panorex (From Coronation Dental Specialty Group, Cambridge, Ontario.)

DIAGNOSTIC APPROACH TO ORAL LESIONS

The first dental exam should begin at the time of tooth eruption approximately at a year of age. As the individual ages, the primary objective of the exam will be the same, the maintenance of the structure, function, and cosmetics of the teeth and mouth. The specifics of the exam, however; will vary over time. As in any evaluation of normal and diseased states, obtaining a complete history is paramount and inclusive of both symptomatic and asymptomatic conditions. Specific to the dental exam, symptoms of mucosal bleeding, ear or jaw pain, mastication difficulties and signs of malocclusion, or improper teeth alignment, and the presence of oral growth should be elicited. Tobacco and alcohol have a significant negative impact on dental health; therefore; eliciting information about their use is critical to the completeness of the oral history.

The physical exam begins with evaluation of the face for symmetry, masses, or skin lesions. An examination of the mouth follows, with inspection of the teeth for alignment, mobility, color, and adherent plaque and tartar. Teeth are gently tapped with the mirror handle to assess percussion sensitivity and manually rocked to determine the presence or absence of mobility. The lips are palpated, with an open mouth and a tongue blade used to guide the examination and increase the visibility of the buccal mucosa, vestibules, palate, uvula, and



Mucous membranes of oral cavity

oropharynx. With the tongue extended, the dorsum of the tongue is exposed and examined; side-to-side motion allows for inspection of both posterolateral surfaces. The ventral surface of the tongue and floor of the mouth is examined with an upward motion of the tongue. Palpation of the vestibules, floor of the mouth, and sublingual and submandibular glands is included in the oral examination. Opening and closing of the jaw while palpating the head of the condyle anterior to the

external auditory meatus allows for assessment of the temporomandibular joint.

Radiographic x-rays complete the dental examination. A panoramic x-ray is useful for a global assessment of the mouth, including but not limited to the presence of cysts or tumors, abnormally absent teeth, or supernumerary teeth. Assessment for dental caries and of the tooth root and bone requires a full set of x-rays, including 14 to 16 periapical and 4 bite-wing films.

CONGENITAL ANOMALIES OF ORAL CAVITY

Median craniofacial malformations include a spectrum of diseases, ranging from agenesis or hypoplasia or insufficient tissue to hyperplasia and excessive tissue, including median anomalies with clefting and normal tissue volume. *Median craniofacial dysplasia* refers to normal tissue volume clefting, which results from an incomplete fusion of facial structures during embryogenesis or gestation. *Cleft lip and/or palate* are the second most common birth anomalies, with a cumulative incidence of 1 per 700 live births varying by race and gender. Although cleft lip and/or palate may occur as part of a congenital syndrome, most often they occur in isolation. Genetics, dietary deficiencies, alcoholism, illicit drugs, medications, maternal infections, and environmental conditions are risk factors in the pathogenesis of these anomalies.

In 1976, Tessier presented a descriptive classification of clefting syndromes, ranging from 0 in the midline of the lower face to 14 in the upper facial midline and proceeding in a counterclockwise direction.

A *true median cleft* is an isolated cleft of the lip with or without insufficient or excessive tissue. In this type of anomaly the cleft passes between the central incisors. The cleft may continue posteriorly to involve the hard or soft palate. The cleft lip, *cheiloschisis*, originates most often at the junction of the maxilla and median nasal process; *unilateral* or *bilateral*, ranging from a notching of the lip margin to a *complete cleft* extending into the nasal fossa. When confined to the lip, it remains a prealveolar cleft, but it may also involve the alveolar ridge and palate (classified as “alveolar” and “postalveolar cleft”). The nose is deviated, with a distinct flattening of the alae of the affected side, and the margin lies at a lower level than the unaffected side. The columella is tilted. If not directly involved in the defect, the alveolar bone may be deformed in its midportion, owing to the deflection of the nasal septum. A flattening of both alae without other deviation or asymmetry is seen in bilateral clefts.

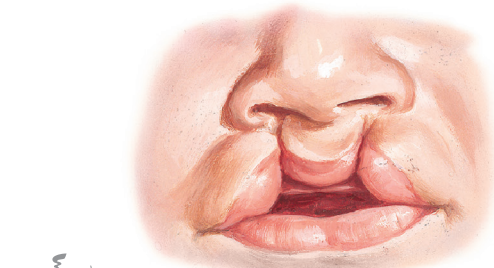
A cleft of the palate (palatoschisis or uranoschisis) may extend from the uvula forward and may involve part or all of the soft and hard palates (respectively, incomplete or complete). It is frequently associated with a cleft of the alveolar process (*gnathoschisis*), which, if complete, separates the premaxilla and the maxilla on one side, with the nasal septum attached to the palatal process of the opposite side. A bilateral alveolar cleft isolates the premaxilla, which is pulled upward and forward and continues as a median cleft of the palate. The nasal septum is free in the midline. The alveolar cleft either usurps the position of the lateral incisor or separates this tooth from the central incisor or cuspid. The dental arch tends to be fairly normal when the alveolar ridge is intact, but extensive clefts show irregular occlusion, with missing, rotated, and misplaced teeth. The alveolar and postalveolar defect interferes with sucking, resulting in aerophagia and nasal regurgitation. Eustachian tube infections, otitis media, labyrinthitis, or hearing impairment are serious conse-



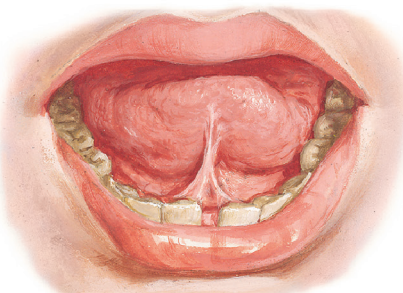
Unilateral cleft lip—partial



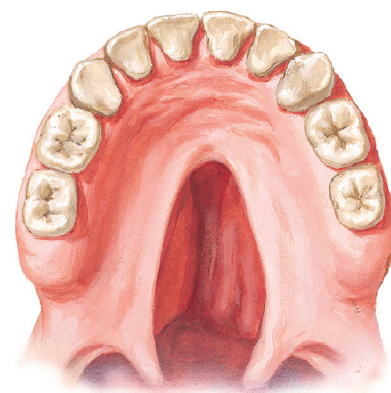
Unilateral cleft of primary palate—complete, involving lip and alveolar ridge



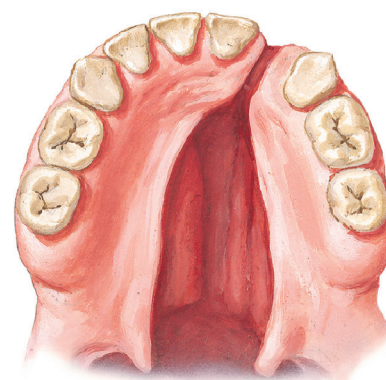
Bilateral cleft lip



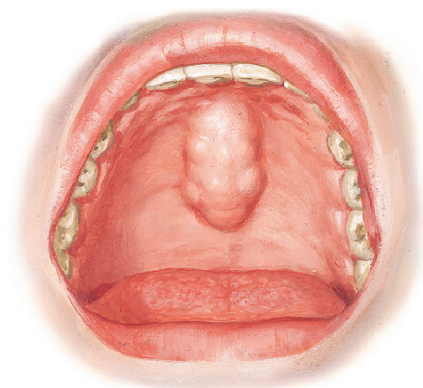
Ankyloglossia—restricted tongue movement from a short lingual frenulum



Partial cleft of palate



Complete cleft of secondary palate and unilateral cleft of primary palate



Torus palatinus—bone deposition on palate

quences that can result from concurrent embryogenesis of the ear canal, complicated by feeding abnormalities. Undernourishment may account for chronic infections and failure to thrive. Failure of palatopharyngeal fusion allows air to escape through the nasal cavity, resulting in speech delays requiring surgical repair. The time of surgical intervention, around the second year, is considerably later than for cleft lip, which occurs much earlier, at 4 to 6 weeks of age.

Ankyloglossia, another congenital abnormality, rarely results from abnormal fusion of the tongue and floor of the mouth but more often as an excessive lingual frenulum attachment. The tongue arches in the midportion rather than protruding beyond the teeth. The degree to which reduced mobility associated with this abnor-

malty results in pain, eating abnormalities, and speech and psychosocial development remains subjective and difficult to characterize. *Torus palatinus* (and, similarly, *torus mandibularis*) is excessive dense bone growth, or exostosis with little or no spongiosa, in an elliptical or nodular shape in the midline of the palate, which is likely a result of both genetic and environmental factors. Development begins in adolescence but may go unnoticed until it interferes with the construction of a denture. *Micrognathia* is a common congenital anomaly of the facial structures resulting in a hypoplastic mandible. Although this is most often associated with a congenital syndrome, it can occur in isolation. It is typically associated with dental abnormalities, specifically poor teeth alignment.

DENTAL ABNORMALITIES

The teeth exhibit many structural abnormalities, which may occur as a result of developmental or genetic alterations or as a result of a systemic process, such as gastroesophageal reflux disease, medications, or environmental and mechanical influences. *Amelogenesis imperfecta* is a developmental disorder of the dentition. It is a rare inherited disorder that results in abnormal formation of tooth enamel on the external layer of the crown of the tooth. The teeth become yellow, brown, or gray and are associated with temperature hypersensitivity, increased calcium deposition, gingival hyperplasia, and an increased risk of dental caries. Restorative dental work with crowns and implants is frequently required.

Hypoplasia of the enamel is produced by defective amelogenesis in the deciduous and permanent teeth and persists unchanged after the enamel is formed. It, therefore, differs fundamentally from caries, erosion, and other acquired lesions. Enamel formation begins in the fifth intrauterine month for deciduous teeth and in the fourth postnatal month for some of the permanent teeth, being completed between 4 and 7 years of age. There are two types of enamel hypoplasia, an inherited form that results from a disturbance in the ectodermal layer during embryogenesis, and an environmental form, which results from systemic infections, disease, and metabolic or nutritional abnormalities.

Hypoplastic tooth enamel has abnormalities ranging from shallow grooves on the smooth enamel to a number of deep grooves or areas in which the underlying dentinal junction is completely exposed, revealing a hard but thin surface. The irregular outline and texture of the lesion distinguish it from a smooth abrasion or erosion, which is more indicative of dental caries. The mechanism of hypoplasia is believed to be either a temporary delay in calcification, resulting in distortion and collapse of an uncalcified matrix, or an actual degeneration of ameloblastic cells.

In contrast to enamel hypoplasia, in which *enamel opacities* may be white, yellow, or brown, *white spots* (*hypomineralization or hypocalcification*) are opaque white well-demarcated round to oval patches on the enamel surface without loss of substance. The cementing substance between the enamel rods is lacking, altering the refractive property of the enamel layer without causing further alterations of the teeth. This condition should not be confused with fluorosis, or “mottled” enamel, which is a hypomineralization of tooth enamel caused by excessive fluoride ingestion. Unlike enamel hypoplasia, fluorosis does not increase the risk for caries, but similar to enamel hypoplasia, it does have aesthetic implications.

Amelogenesis imperfecta is a very rare hereditary hypoplasia of enamel. In one of the two types described, enamel is completely missing (agenesis), and in the other, the enamel matrix is laid down but fails to calcify. Both deciduous and permanent teeth are affected. Such enamel is soft and may be easily broken away from the dentin by normal wear or by an instrument. Consequently, there are intact crowns on recently erupted teeth but progressive deterioration of the enamel on



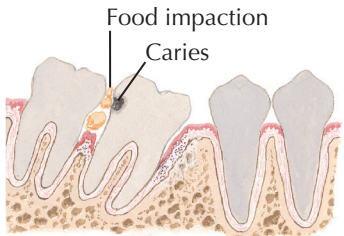
Enamel hypoplasia



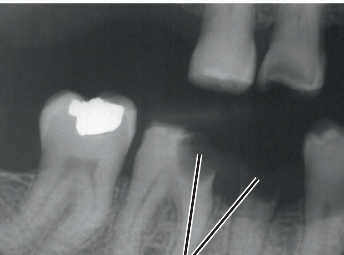
Hypomineralization of enamel



Dentinogenesis imperfecta (opalescent dentin)

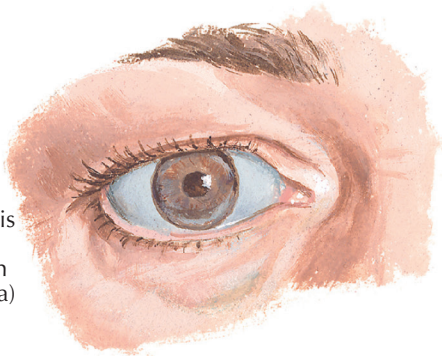


Migration of teeth from missing teeth



Dental caries

Blue sclera in osteogenesis imperfecta (often but not invariably associated with dentinogenesis imperfecta)



Amelogenesis imperfecta

F. Netter M.D.

previously erupted teeth. With aging, very little enamel is left, being only visible at the cervical line. The soft dentin is whitish gray and rapidly discolors further, and is worn down to stumps from years of mastication. Consequently, teeth are typically small, with multiple pits and grooves causing rapid deterioration of the teeth and significant tooth loss.

Dentinogenesis imperfecta (opalescent dentin), represents a group of hereditary disorders that result in abnormal dentin formation in both deciduous and permanent

teeth. The crowns of the teeth are of normal dimension with stunted roots. The pulp canals are markedly reduced in size or completely obliterated. The color of the teeth as they erupt ranges from slightly pink to darker bluish or brownish gray. There is a tendency of the enamel to fracture and peel away owing to defective dentin, leaving an atypical, amber-brown dentin that is translucent or opalescent. The teeth show rapid wear. Sensitivity is lacking because of continual deposition of secondary dentin in the pulp. A dystrophic arrangement

DENTAL ABNORMALITIES

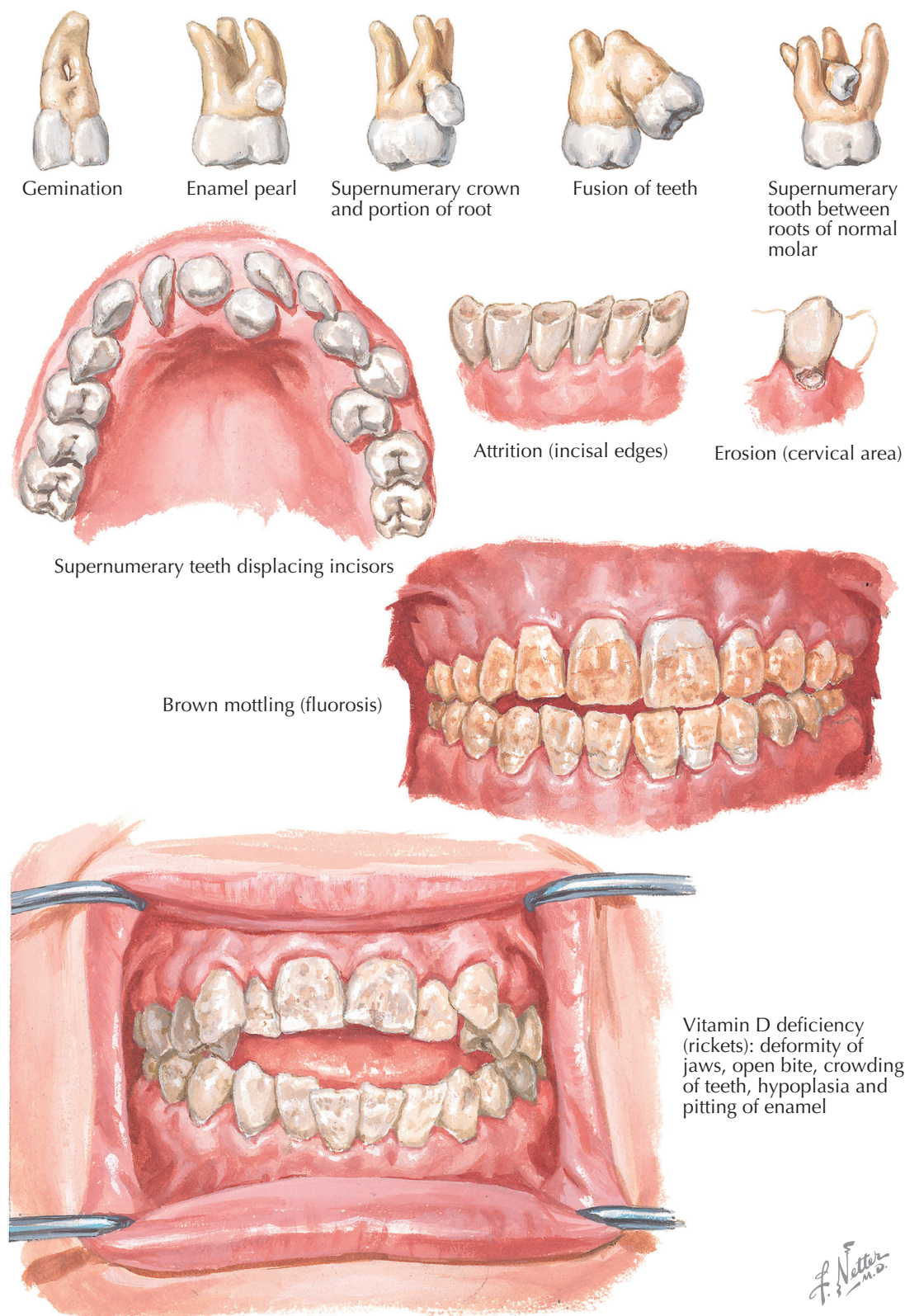
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of dentinal tubules and abnormal blood supply via canals that penetrate the dentinal substance and impart the brownish color are characteristic. This condition may be part of a generalized osteogenesis imperfecta, characterized by brittle bones and *blue sclerae*.

Gemination is the production of twin teeth from one enamel organ. The epithelium of the enamel organ invaginates as though to produce two separate teeth. If this abortive fission is symmetric, the result is a bifid tooth, with fully developed crowns and confluent roots. Asymmetric division gives rise to a smaller accessory tooth or component. When the gemination process is multiple, the designation *odontoma* should apply. A *fused tooth* is more common in the deciduous dentition, differing from twin teeth in that some physical pressure has caused a joining of young tooth germs (both enamel organ and dental papilla). If the fusion is late, only the roots may be joined, because the crowns have already developed. *Supernumerary teeth*, which are wholly formed, are usually due to hyperplasia of the dental lamina, forming extra tooth germs. Such a tooth may be normal in shape, peg shaped, or of rudimentary size, lying *between the roots of a normal molar*. A *supernumerary cusp* or *root*, including the *enamel pearl*, on the other hand, is formed by local hyperplasia of the tooth germ, or, in some cases, of invagination of the dental epithelium as in geminated teeth.

Destruction of the tooth surface by mechanical forces, whether from coarse abrasive foods, bruxism (teeth grinding), tooth brushing, or certain occupations, such as holding nails between the teeth, is referred to as *abrasion*. The term *attrition* is used for the natural wear of incisal and occlusal surfaces, whereas abrasion from tooth brushing primarily affects the cervical parts of cuspid and bicuspid teeth. *Erosion* is a chemical process that may, at times, produce lesions that are indistinguishable from abrasive lesions. Affected individuals, typically in their thirties or older, develop wedge- or spoon-shaped erosions on the labial and buccal surfaces, primarily on the gingival margins, from alterations of saliva presumably acting in an enzymatic fashion. The lesions are usually smooth, similar to abrasions, but rough pitted lesions have also been seen. Gastroesophageal reflux with proximal extension to the oral cavity can displace saliva, leaving the surfaces of the tooth bare and thereby permitting pepsin, a proteolytic enzyme, to act on and remove the protective dental pellicle. Once this protective layer is destroyed, the acid is permitted to interact with enamel and the hydrogen ion can begin to dissolve the enamel. The degree and rate of dissolution are affected by the ratio of acidity to buffering near the tooth. Erosive disease affects tooth sensitivity, tooth stability, and aesthetics. Similar damage can be seen with the excessive ingestion of acidic foods and liquids.

Fluorosis, or *mottled enamel*, is an endemic lesion in geographic areas where the content of fluoride ion in the drinking water exceeds 2 parts per million. It occurs



only in individuals exposed to high concentrations of fluorine during enamel formation prior to tooth eruption (young children and early adolescents). Affected teeth range in appearance from a hard and glazed surface with small chalky spots, to wider paper-white areas or striations, to pitted and irregularly marred or excoriated and mottled color changes of chalky white and shades of brown from yellow to almost black.

Dentition is almost universally affected by aging; the teeth begin to yellow or darken in color owing to

thinning of the dentin that lies under the surface enamel. *Dental caries*, commonly referred to as tooth decay, is a bacterial infection resulting in demineralization and destruction of the hard surfaces of the teeth, specifically the enamel, dentin, and cementum. The bacteria produce acidity through the fermentation of food debris on the teeth. *Streptococcus mutans* has been identified in the plaque and saliva in teeth laden with dental caries; its presence in this environment suggests a causative role in the pathogenesis of dental caries.

PERIODONTAL DISEASE

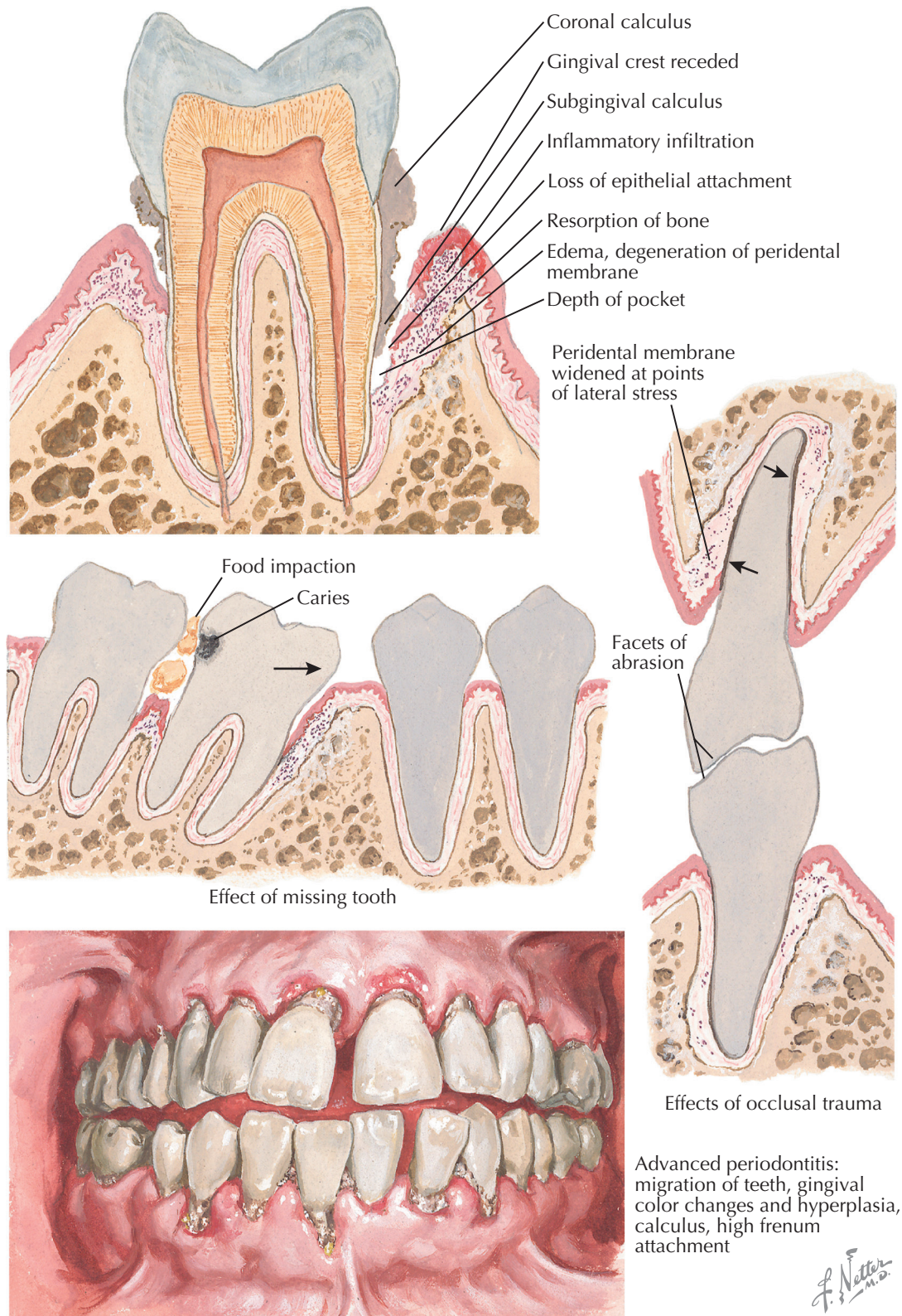
Disease of the periodontal tissues constitutes the chief reason, more prevalent even than dental caries, for the loss of teeth. It is almost universally present among adults. Epidemiologic studies have shown an association between the development of coronary artery disease and the presence of periodontal disease. This is presumed to be independent of the close association between tobacco smoking and each of these conditions.

Periodontitis manifests as a chronic inflammation resulting from endogenous plaque bacteria, which arise from a worsening gingivitis culminating in the loss of dentition. A *marginal periodontitis* is usually the sequel to long-standing marginal gingivitis and generally includes all the signs of marginal gingivitis plus alveolar *crestal bone* and adjacent *periodontal membrane* resorption. The formation of a periodontal pocket, a pathologic alteration of the gingival attachment, is pathognomonic for this condition. Periodontal disease is defined by pocket depth and loss of attachment. The epithelial lining of the gingival crevice is ulcerated, and the periodontal membrane fibers are destroyed, generating an inflammatory cell infiltrate in the corium which may produce a purulent discharge. The epithelial attachment is displaced and takes successively deeper positions as the pocket increases. Beginning with notching of the alveolar crest, bone resorption continues, with destruction of the cribriform plate (lamina dura). Under the influence of occlusal trauma, the pocket penetrates toward the apex of the root; such pocket formation is seen in radiographic images as "vertical" in type, indicating advanced periodontal disease, compared with the simpler "horizontal" resorption. The local factors that contribute to the development of these pockets include deposition of plaque and calculi from saliva; food debris, which creates an environment for incubation of bacteria and a resulting microbiofilm in the mouth; poor oral hygiene; and mouth breathing. Tobacco is the most significant risk factor associated with the development of periodontal disease. Patients with diabetes mellitus, HIV infection, or cancer or who have undergone radiation therapy to the head and neck region are also at increased risk for periodontal disease. Medications that reduce salivary production can also contribute to the development of this condition. Some individuals are genetically susceptible to the development of periodontal disease; when they also have other high-risk factors, there is a greater likelihood of the development of severe periodontal disease.

Eighty-five percent of patients with periodontitis have mild disease, and less than 5% have aggressive periodontitis. Rapidly progressive chronic periodontitis can develop in young children, resulting in bone and possibly tooth loss by early adulthood. Aggressive periodontitis in healthy adolescents is typically a result of colonization by *Aggregatibacter actinomycetemcomitans*. A less common form of aggressive periodontitis affects the deciduous teeth, resulting in acute proliferative gingivitis with rapid alveolar destruction, which resolves before the eruption of the permanent teeth.

HIV infection is associated with a particularly virulent form of rapidly progressive periodontitis (see Plate 2-53).

Occlusal trauma, most often as a result of grinding (bruxism), clenching, or similar habits producing repetitive and excessive contacts of tooth on tooth, can result in an augmentation of lateral stresses on a tooth. The malpositioned, nonfunctional contacts result in dental abrasions on the surfaces and a widening of the



periodontal membrane within the infrabony pockets, leading to tooth mobility.

A *missing tooth* permits an open contact, with food impaction causing an interproximal pocket, typically associated with caries on the distal tooth surface. The stress of occlusion on such a tooth may further accelerate the formation of a pocket on the mesial surface.

Migration of teeth, a late symptom in periodontitis, is a consequence of open contacts, wedging of food particles, extrusion of teeth through the pressure of granulation tissues, and other traumatic relationships in the

deranged occlusion. Mobility of the teeth becomes marked as bone resorption increases the ratio of dental parts supported by bone to those not supported. The gingiva in this phase of periodontitis is typically soft and spongy and is dusky in color than normal, and there is retraction of the margin and abundant accretions of calculus.

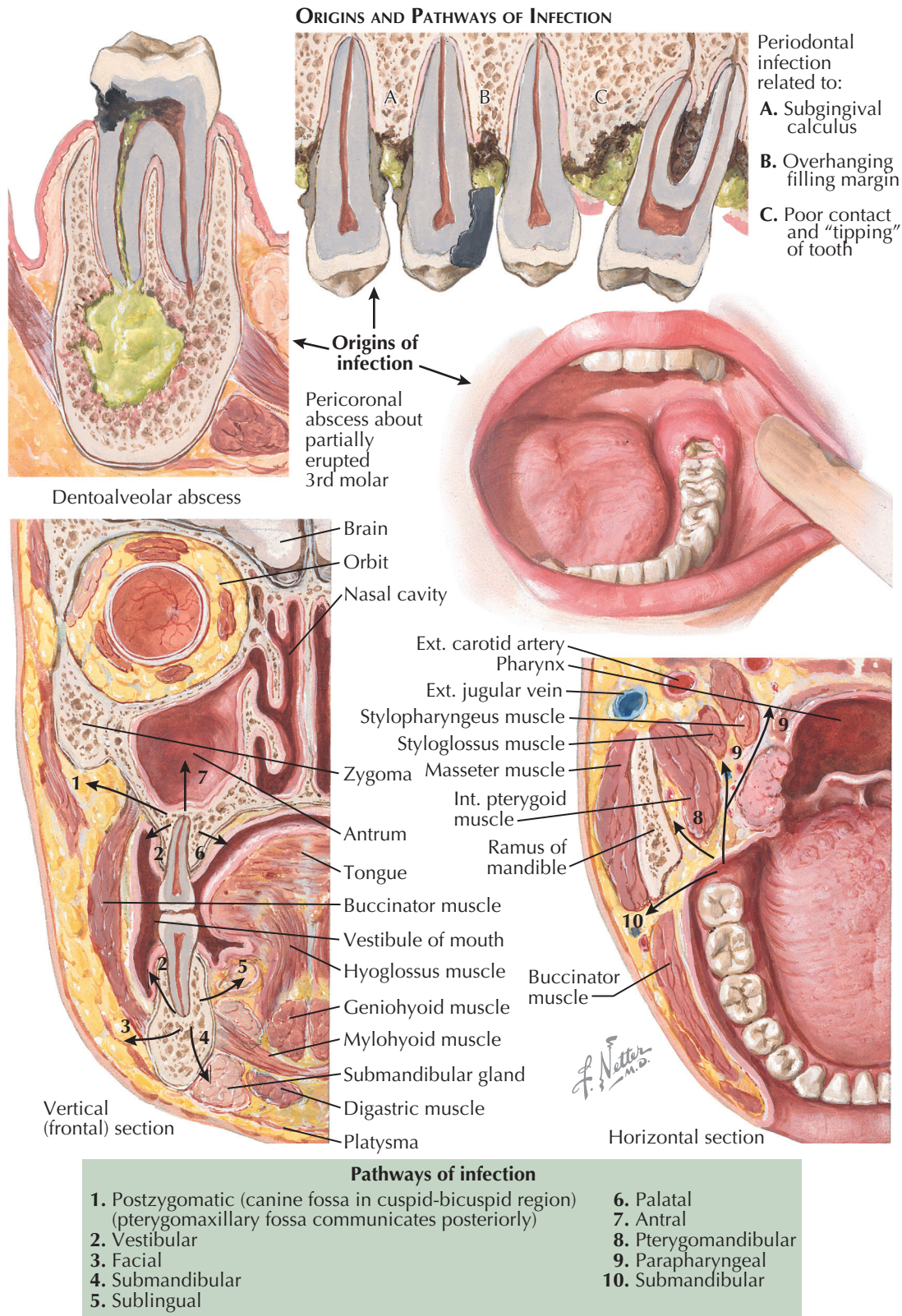
Regardless of disease severity, the initial phase of treatment requires removal of plaque and calculus deposits through professional scaling and root planing, followed by proper oral hygiene.

**ODONTOGENIC INFECTIONS:
THEIR SPREAD AND ABSCESS
FORMATION**

The most frequent causes of inflammatory swellings of the jaws, the middle and lower thirds of the face, and the upper part of the neck are infections of the teeth, with the pulp canal or the periodontal membrane as the primary focus. The *dentoalveolar abscess* is the most frequently encountered dental infection. It is usually the end result of dental caries; more rarely, it originates in a tooth devitalized by trauma. The abscess may develop very acutely and burrow through bone to lodge under the periosteum, which it then perforates to induce an intraoral or a facial abscess. In other instances, a more chronic inflammatory process leads to an organized granuloma at the root apex, which may remain dormant for years, evolve slowly into a sterile cyst, or develop into an acute alveolar abscess. While the abscess is confined to the bone, pain and extreme tenderness of the involved tooth are the characteristic symptoms. By the pressure of edema, the tooth is extruded from its socket, so that each contact with the teeth of the opposing jaw aggravates the pain.

The *periodontal abscess* is the second most common odontogenic infection. It arises from an ulcerated periodontal crevice (pocket), which is created by the loss of attachment (*poor contact*) between the tooth on one side and the investing gingiva, periodontal membrane, and bone on the other. This periodontitis occurs with increasing severity in older age groups and is the most prominent etiologic factor in the loss of teeth. *Calculus deposits*, traumatic occlusion, *irritating filling margins*, *implanted teeth*, and other factors may play a contributing role. A third odontogenic infection, the *pericoronal abscess*, originates in a traumatized or otherwise inflamed flap of gingiva overlying a partly erupted tooth, usually a lower third molar.

Odontogenic infections involve the soft tissues chiefly by *direct continuity* (the numbered pathways are illustrated in the drawings). Lymphatic spread plays a secondary role, and hematogenous dissemination rarely results in a facial abscess. Bacteremia, however, is common and has been demonstrated as a transient phenomenon arising from chewing or manipulation of apically or periodontally infected teeth. Local extension follows the line of minimal resistance chosen based on the tooth and its anatomic proximity to the bone, fascia, and muscle attachment. Where the muscle layers act as a barrier, extensive cellulitis may spread along the fascial planes of the head and neck. Infections from the maxillary teeth may perforate the cortical bone of the palate, the vestibule, or the regions separated from the mouth by attachments of the muscles of facial expression or the buccinator muscle. Those from the incisor teeth tend to involve the upper lip; from the cuspids and premolars, the canine fossa; and from the molar teeth, the infratemporal space or mucobuccal fold. The *vestibular abscess* is generally localized and is not accompanied by excessive edema, owing to the softness of the tissues and lack of tension. In the advanced stage, a shiny fluctuant swelling is visible at the region of the root apex or somewhat below it. *Abscess (postzygomatic) of the canine fossa* usually bulges into the buccal sulcus but is chiefly marked by swelling of the infraorbital region of the face and the lower eyelid. The upper lid, the side of the nose, and the nasolabial fold and upper lip may be involved by edema.



Infections of the mandibular teeth may give rise to swellings of the *vestibule* or the sublingual, submental, or submandibular space. *Abscess of the submandibular region* is encountered with infections of the premolar and molar teeth. The classic sign is a large visible swelling below the mandible, extending to the face and distorting the lower mandibular border; it is extremely tender and accompanied by trismus. A submandibular space abscess may easily pass into the sublingual space

(5) along the portion of the gland that perforates the mylohyoid muscle. This results in elevation of the floor of the mouth and displacement of the tongue to one side. The submental area may be invaded by passage of pus past the digastric muscle, resulting in a general swelling of the entire submandibular region. A dentoalveolar abscess from a lower molar tooth is capable of producing the most serious and fulminating infections of the submandibular (4), pterygomandibular (8), and

ODONTOGENIC INFECTIONS: THEIR SPREAD AND ABSCESS FORMATION (Continued)

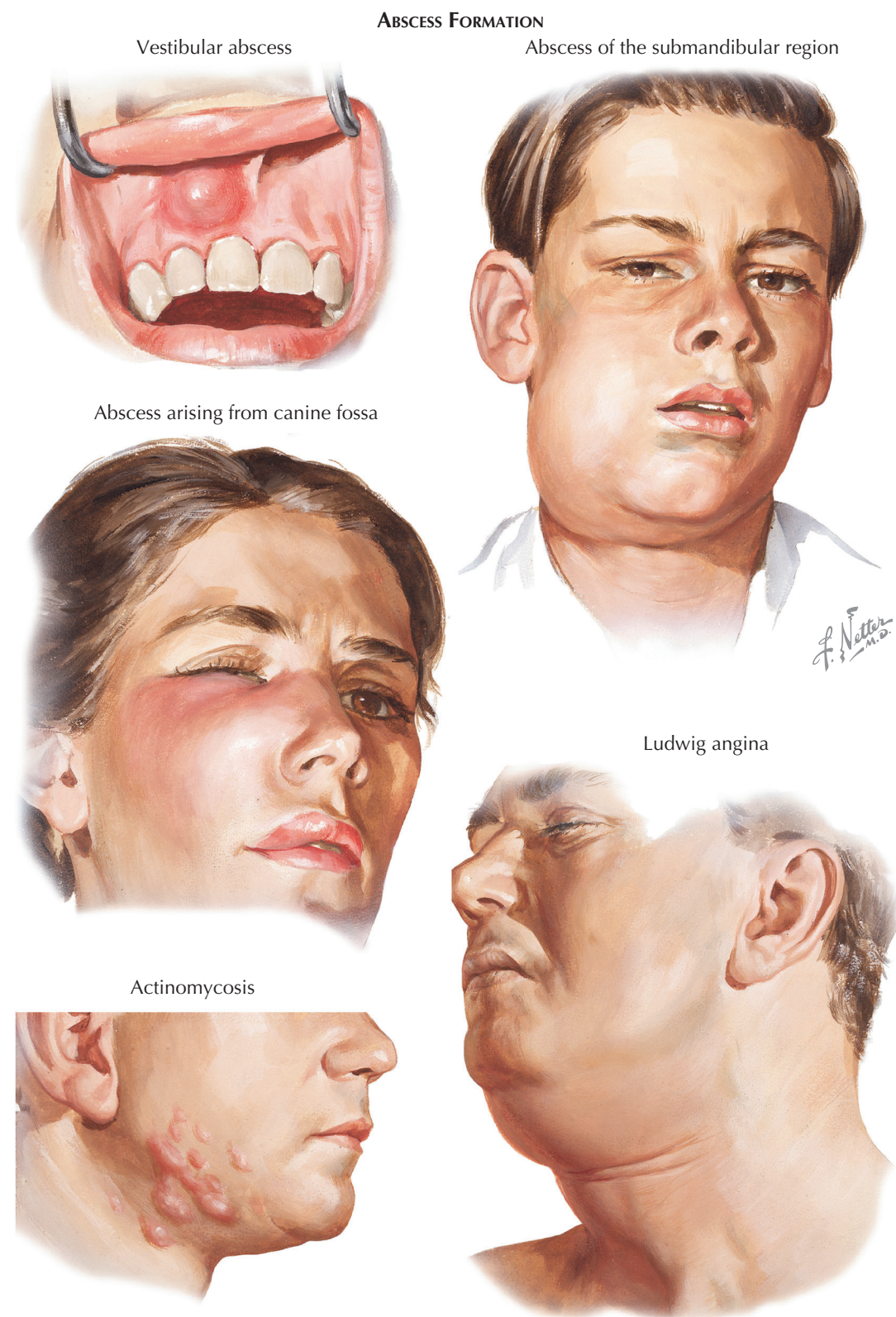
parapharyngeal (9) pathways. A pterygomandibular abscess results in deep-seated pain and extreme trismus, with some deviation of the jaw owing to pterygoid muscle infiltration. Infection in this space may, in exceptional cases, enter the pterygoid and pharyngeal plexuses of veins and result in a cavernous sinus thrombosis. A parapharyngeal abscess causes bulging of the pharynx, with equally marked trismus.

The onset of *facial cellulitis* is heralded by edema of the soft parts, often quite extensive and without discernible fluctuation. Pain increases with pressure and induration. As abscess formation progresses, the central area reveals pitting edema and eventually becomes shiny, red, and superficially fluctuant. Pain and tenderness are related to pressure and induration. A fever of 38.5° to 40°C, leukocytosis, and severe toxemia are characteristic. Trismus occurs when the elevator muscles are affected by inflammation or reflex spasm caused by pain. In some cases, rather than the typical production of an abscess, a chronic cellulitis follows the acute phase, with persistent, deeply attached swelling. A phlegmon may be apparent from the onset, with a brawny, indurated distention of muscular and subcutaneous layers, devoid of exudate and showing no tendency to localize.

Ludwig angina, a purulent inflammation, begins as a phlegmon in the submandibular space, usually after a molar tooth infection or extraction, and rapidly spreads to occupy the submandibular region, bounded inferiorly by the hyoid bone. The floor of the mouth and tongue are raised through infiltration of extrinsic and intrinsic muscles. The hard, dusky swelling descends to the larynx, where edema of the glottis, combined with the pressure of the tongue against the pharynx, interferes with respiration. In addition to the usual flora of odontogenic infections (alpha, beta, and gamma streptococci and, occasionally, gram-negative bacilli), the bacterial picture in true phlegmon tends toward anaerobic organisms, or facultative anaerobes, and gangrene-producing mixed groups such as the fusospirochetal combination.

Osteomyelitis may produce cellulitis or abscess similar to the odontogenic variety. Its chief incidence is as a complication following a traumatic extraction, particularly if performed in the presence of acute infection, or a comminuted fracture involving the roots of teeth. Occasionally, it is the result of an abscess contiguous to a large area of bone, and it typically begins in the lower third molar region. Sclerotic or dense bone is more easily deprived of nutrition through trauma and at increased risk for developing an abscess following tooth extraction. Symptoms include those of cellulitis, with intermittent, deep, boring pain, and sequestrum and involucrum formation, seen on radiographic imaging in late stages. Symptom and radiographic resolution results from therapeutic intervention with abscess drainage and antibiotic therapy.

A *fracture of the mandible or maxilla* is always compound where teeth are present, causing the line of fracture to be contaminated by normal oral flora that seldom produces infection; however, with projection of



a tooth root in the line of fracture, suppuration typically develops. An externally compounded fracture is more prone to develop sepsis than a noncomminuted or simple nondisplaced fracture.

Actinomycosis is a specific infection that occurs centrally in the jaws or peripherally in the soft tissues, where it forms an indurated swelling with multiple fistulae of the skin, resembling a chronic odontogenic abscess. Because this is an obligatory oral pathogen,

inoculation is usually through damaged mucosa, most often following oral surgery or recent dental work and less often following trauma or local radiation therapy. The diagnosis is chiefly made by a smear of the exudate, which contains peculiar granular yellow bodies (*sulfur granules*) and the specific organism (*Actinomyces bovis*) that causes the disease. Culture of the organism is unreliable, and biopsy may be required to establish the diagnosis.

GINGIVITIS

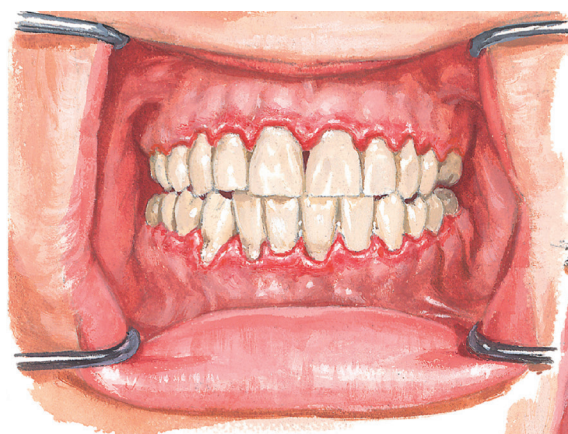
Marginal gingivitis is chiefly caused by local irritating factors, such as calcareous deposits on the teeth, food impaction, rough or overhanging filling margins and other dental restorations, misalignment of teeth, open contacts or other morphologic faults causing improper function, and hygienic neglect. These factors are, of course, complicated by such conditions as allergies, mouth breathing, medications, tobacco smoking, and hormonal changes. As with periodontal disease, individuals may be genetically predisposed to the development of this condition. Marginal gingivitis is the first stage in a complex periodontal syndrome that is further characterized by pocket formation and inflammation of the investing tissues (periodontitis) and, finally, by periodontal abscesses (see Plate 2-36). Clinically, the gingiva is conspicuous for a shiny pink, red, or even cyanotic surface, edema, and a strong bleeding tendency of the margins and papillae of the gum. In the initial stages of the condition, there is a deepening of the sulcus between the tooth and the gingiva; this is followed by a band of erythema, indicative of the inflamed gingiva, which can be along one or, most often, multiple teeth, resulting in edema of the interdental papillae that easily induces bleeding.

Hypertrophic gingivitis describes a frequent variation of the marginal type of inflammation, depending upon the individual response and the chronicity. An increase in size of the papillae is more noticeable than that of the free margin of gum and is especially related to accretions of calculus on the teeth. Hormonal alterations, as in menstruation, pregnancy, and menopause, will increase the degree of hypertrophy. Diffuse, idiopathic fibromatosis of the gingiva, which is free of inflammation, is normal in color, and presents a uniform proliferation of the gingiva in a firm, bulging mass throughout the jaw, is another form of hypertrophic gingivitis; it is similar to the gingival hyperplasia resulting from use of phenytoin.

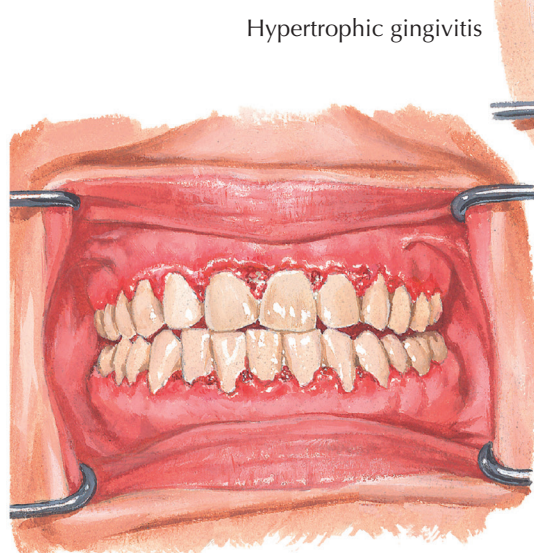
Although the most common form of gingivitis, *plaque-induced gingivitis*, is limited to gingivitis associated with dental plaque and is distinct from other presentations of gingivitis, the bacterial plaque initiates the host response. The plaque accumulates in the interdental gaps, the gingival grooves, and plaque traps that harbor plaque. The bacteria in the plaque activate lipopolysaccharides or lipoteichoic acid, which promotes the inflammatory response causing gingival hyperplasia. As the disease progresses, the bacterial situation becomes more complex, with an increase in numbers and types of bacteria present.

Necrotizing ulcerative gingivitis, or fusospirochetal gingivitis, commonly known as trench mouth, is a noncontagious opportunistic infection caused by bacteria indigenous to the mouth in a host with reduced tissue resistance. Predisposing factors include tobacco smoking, viral respiratory illnesses, poor nutritional status, psychological stress, and immunocompromised states such as HIV/AIDS. Chemoradiation therapy may also be a predisposing factor. Local causes include all conditions promoting growth of anaerobic organisms, such as gum flaps over third molar teeth, crowded and malpositioned teeth, inadequate contact areas, food impaction areas, and poor oral hygiene.

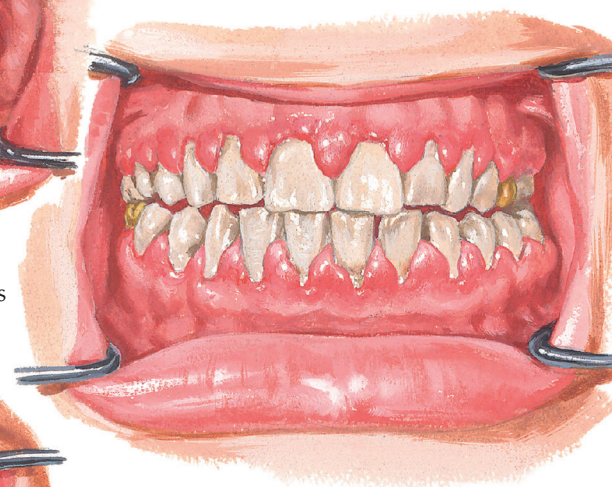
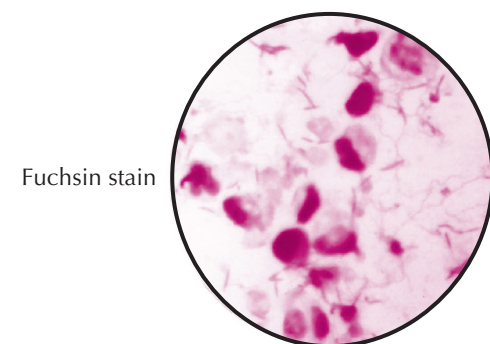
The flora of necrotizing ulcerating stomatitis typically includes one or more types of spirochetes and a fusiform bacillus. Ulceration and pseudomembrane formation are the specific lesions seen in this condition.



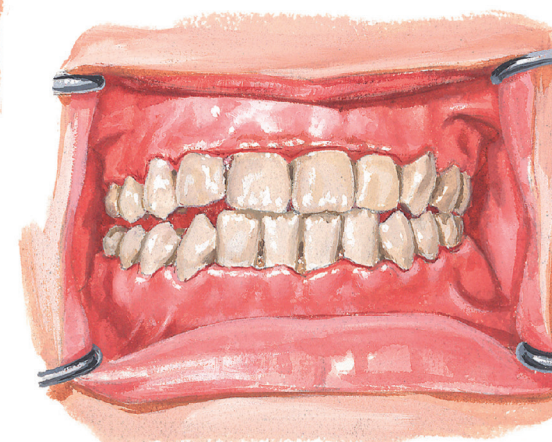
Marginal gingivitis



Hypertrophic gingivitis

Acute fusospirochetal gingivitis
(Vincent infection)

Fuchsin stain

Smear: fusiform bacilli and spirochetes
characteristic of Vincent infection

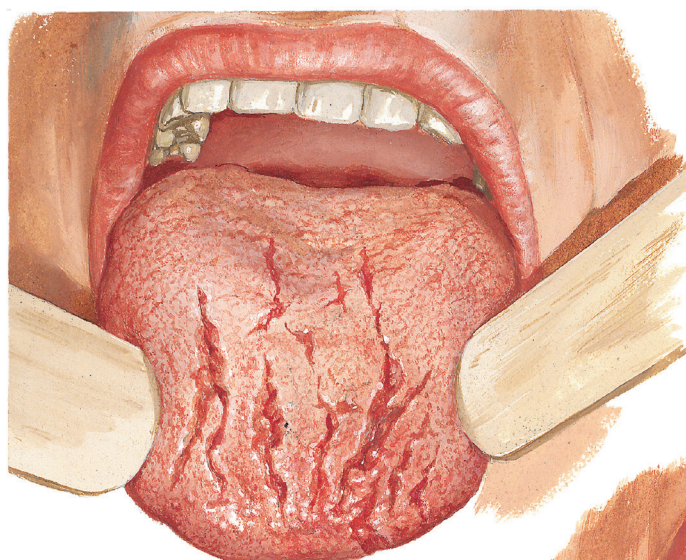
Chronic fusospirochetal gingivitis

F. Netter M.D.

The acute form presents with a sudden onset of oral pain and constitutional symptoms of elevated temperature and malaise; it is more often seen in children or immunocompromised individuals. Submandibular lymphadenopathy is variable. Severe pain, a strong characteristic, malodorous breath, and gingival bleeding are marked; objectively, these signs are related to flat, punched-out, grayish ulcers, which erode the tips of the papillary gingivae and spread to the margins, which are covered by a thin diphtheritic-like membrane. On slight pressure, bleeding may occur from all affected areas. In severe cases the lesions spread to the tongue, palate, pharynx, and tonsils; profuse salivation, a thickly coated tongue, and bleeding are seen.

Chronic necrotizing gingivitis is a milder form of this disease; it exists from the outset or is a slowed-down phase of the acute form. Subjective symptoms are much reduced. The first awareness is of bleeding when brushing the teeth. Careful retraction of the papillae may be necessary to reveal the typical necrosis. Pain is usually absent. The typical odor develops later because destruction proceeds slowly. The response to therapy is far slower in long-established cases, and recurrence is a constant hazard. As the architecture of the gingiva is altered, anaerobic areas are created and food retention is abetted, so that therapy against the infection alone is of only momentary value; it must be directed to a restoration of the proper gingival form.

FISSURED TONGUE, HAIRY TONGUE, MEDIAN RHOMBOID GLOSSITIS

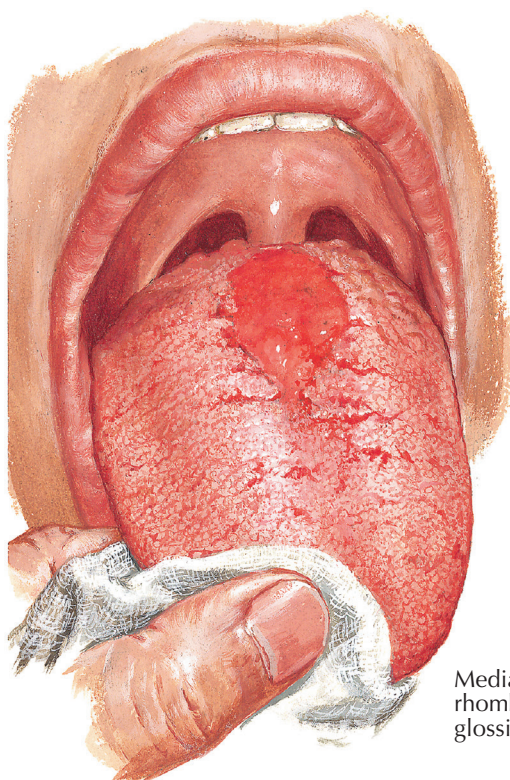


Fissured tongue

MANIFESTATIONS OF DISEASE OF TONGUE

As a consequence of the easy accessibility to clinical inspection, the tongue, in the course of medical history, has played a rather special role as a diagnostic indicator of systemic disease. The degree of moisture or dryness of the lingual mucosa may indicate disturbances of fluid balance. Changes in color and the appearance of edema, swelling, ulcers, and inflammation or atrophy of the lingual papillae may represent signs of endocrine, nutritional, hematologic, metabolic, or hepatic disorders, infectious diseases, or aberrant ingestions. On the other hand, it should be recognized that the tongue participates with the gingivae and the buccal mucosa in localized pathologic processes of the oral cavity, and that a number of conditions exist in which the surface or the parenchyma of the tongue itself is exclusively involved.

Fissured tongue is a congenital lingual defect, also called a grooved or scrotal tongue, characterized by deep depressions or furrows, which run primarily in a longitudinal direction starting near the tip and disappearing gradually at the posterior third of the dorsum. Both the length and depth of the furrows vary and can best be demonstrated by stretching the tongue laterally with tongue blades. It has often been observed that the fissures form a leaflike pattern, with a median crack larger than the other furrows. In general, the larger grooves run parallel, with smaller branches directed toward the margin of the tongue. The mucosal lining of the crevices is smooth and devoid of papillae. Most often this condition is asymptomatic; rarely, symptoms are reported, which include mild discomfort when eating spicy or acidic foods or drinks. Occasionally a fissured tongue is incidentally noted in an individual that also has macroglossia or a geographic tongue; there is, however, no intrinsic relationship between these three lingual conditions. *Median rhomboid glossitis* is a misnomer, because it is not an inflammatory process but a developmental lesion resulting from failure of the lateral segments of the tongue to fuse completely before interposition of the fetal tuberculum impar. It is an oval or rhomboidal, red, slightly elevated area, about 1 cm in width and 2 or 3 cm long, contrasting in color with the surrounding parts of the dorsum. This area is devoid of papillae. Sometimes it may be nodular, mammillated, or fissured. Except for an occasional secondary inflammation, it causes no subjective symptoms. Visual



Median rhomboid glossitis

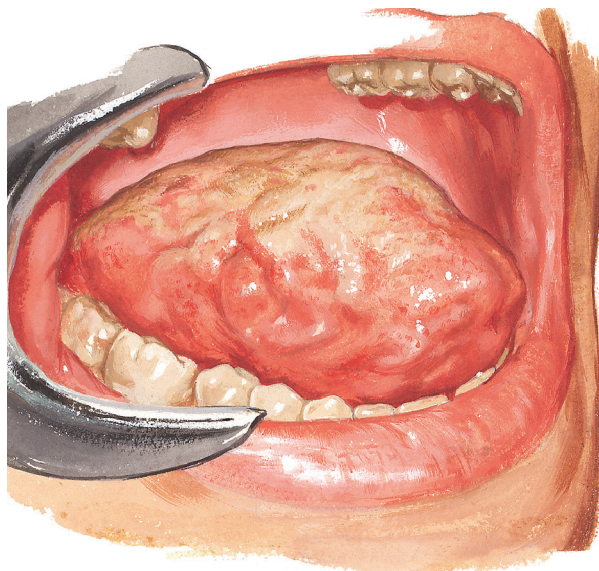


Hairy tongue

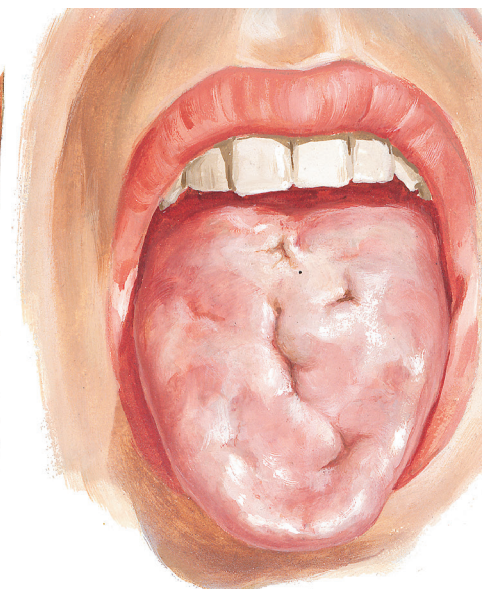
confirmation of this benign lesion will differentiate it from a malignant process, thereby avoiding an unnecessary and costly evaluation. *Geographic tongue*, otherwise labeled erythema migrans or Butlin's wandering rash, is a chronic superficial desquamation of obscure etiology seen most often in children. It may, however, recur at intervals throughout life or persist unchanged in degree. The rash is confined to the dorsum of the tongue and appears, rarely, on the inferior surface. The dorsal surface is marked with irregular, denuded grayish

patches, from which, at times, the papillae are shed to reveal a dark-red circle of smooth epithelium bordered by a whitish or yellow periphery of altered papillae, which have changed from normal color and are about to be shed in turn. The circles enlarge, intersect, and produce a maplike configuration. The lesions appear depressed compared with the papillated surface and clearly demarcated. Continued observation, which reveals the migratory character of the spots, is necessary to confirm the diagnosis. The geographic tongue may

AMYLOID TONGUE, LUTETIC GLOSSITIS, GEOGRAPHIC TONGUE, MEGALOGLOSSIA



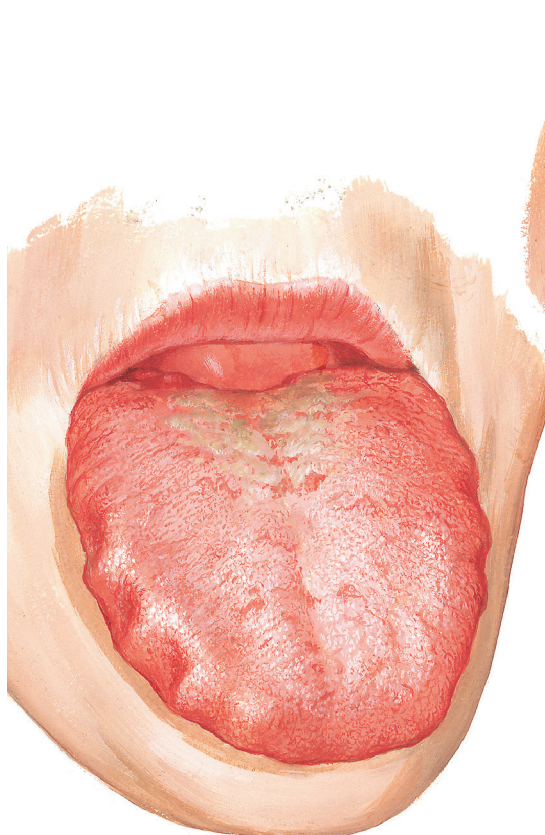
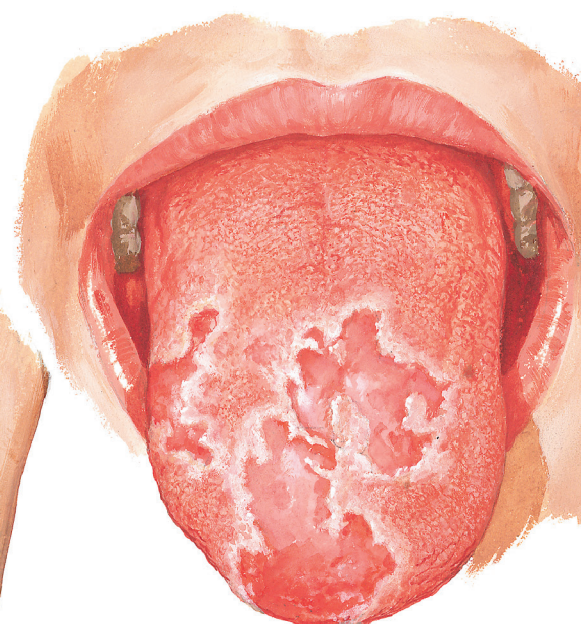
Amyloid tongue

Luetic glossitis
("glass tongue")MANIFESTATIONS OF DISEASE IN
THE TONGUE (Continued)

sometimes be fissured or lobulated at the margin, where it contacts the teeth. *Hairy tongue*, or black tongue, is an acquired discoloration. Thick, yellowish, brownish, or black furry patches, made up of densely matted, hypertrophied filiform papillae, sometimes cover more than half of the dorsal linguae. The surface of the tongue is normally coated with a layer of papillae that serve as taste buds. The tongue also has a protective layer of dead cells known as keratin. Hairy tongue results because of defective desquamation of the keratin overlying the papillae. Normally, the amount of keratin produced equals the amount of keratin that is swallowed with food. The balance is disrupted when there is an increase in keratin production or a decrease in swallowed keratin. The keratin or dead cells and the papillae grow and lengthen rather than being shed, creating hairlike projections that are subjected to entrapment and staining by food, liquids, tobacco, bacteria, and yeast.

Megaloglossia is, on rare occasions, an isolated congenital anomaly. An acute form is caused by septic infections and by giant urticaria. The chronic form is a result of lymphangioma or hemangioma, or a secondary effect of Down syndrome, acromegaly, or myxedema. (It can also be produced by tumors, syphilis, and tuberculosis.) In myxedema, the tongue enlarges, resulting in thick speech and difficulty with mastication and swallowing. The margins are typically lobulated from the pressure or confinement against the teeth.

Luetic glossitis has been variously called bald or glazed luetic tongue, sclerous or interstitial glossitis, or lobulated syphilitic tongue. The clinical appearance depends on the extent of gummatous destruction, which may be superficial or deep, causing an endarteritis with a smooth, atrophic surface. Hyperkeratosis may also be evident. On palpation various degrees of fibrous induration are detected in the relaxed tongue. The surface is thrown into ridges, grooves, and lobulations, with a pattern of scars that may assume a leukoplakic appearance. The induration and scarring are a direct result of the gummas. The smooth, depapillated, "varnished" surface is, strictly speaking, an atrophic symptom seen in advanced forms of anemias, vitamin B deficiency, celiac sprue, Plummer-Vinson syndrome, and prolonged cachectic states.

Megaloglossia
(in myxedema)

Geographic tongue

An *amyloid tongue* is usually a part of a generalized amyloidosis. Only occasionally are isolated amyloid deposits found in the base of the tongue without a generalized disease. The tongue, as illustrated here, has been heavily infiltrated, together with the liver, spleen, and other mesodermal organs, in a generalized secondary amyloidosis resulting from a multiple myeloma. Amyloid deposition causes a hyaline swelling of connective tissue fibers, with accumulation of waxlike material

and obliteration of vessels through thickening of their walls. Clinically, the tongue is enlarged and has mottled dark-purple areas with translucent matter. Furrows and lobules cover the denuded dorsum. The diagnosis is easily ascertained by a biopsy specimen, which shows the typical brown color when exposed to Lugol solution and turns blue when sulfuric acid is added. Lugol solution will also elicit the diagnostic reaction if it is introduced into a small lingual incision in situ.

J. Netter M.D.

LEUKOPLAKIA

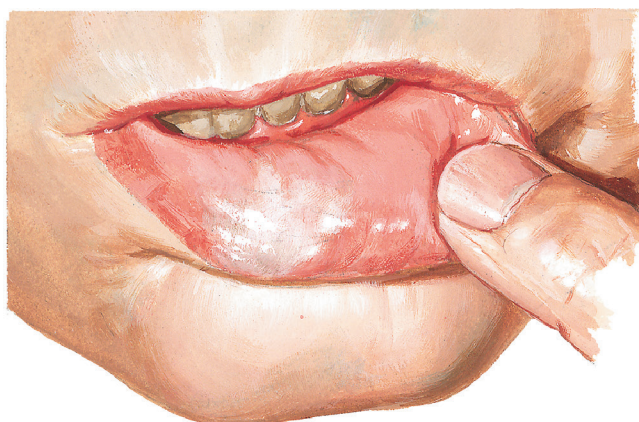
Although *oral leukoplakia* is often a benign reactive process, it can also represent a precancerous lesion, appearing as white plaques consisting of hyperplastic squamous epithelium, in the initial step in the malignant transformation process from hyperplasia to dysplasia and finally to squamous cell carcinoma. Over a 10-year period, 1% to 20% of leukoplakia lesions will progress to squamous cell carcinoma. There is a decreased risk of malignant transformation in areas of thick mucosa, such as the dorsum of the tongue or cheek, and an increased risk in areas of thin mucosa, such as the ventral aspect of the tongue. The prevalence of leukoplakia in the United States is less than 1% of the population. The strongest risk factor for the development of leukoplakia is tobacco use. Alcohol use, ill-fitting dentures, and other restorative dental appliances, age over 40, male gender, and lower socioeconomic status are also associated with an increased risk of malignant transformation. When seen in association with inflammatory conditions, it is purely an inflammatory reaction, with no risk of malignant transformation. An association between the development of leukoplakia and human papillomavirus or *Candida albicans* has been established. Leukoplakia on the dorsal surface of the tongue can be seen in tertiary syphilis. Iron, folate, and vitamin B₁₂ deficiencies may result in a disruption in epithelial differentiation, increasing the risk of leukoplakia. Most lesions are asymptomatic; biopsy is required to differentiate benign from malignant disease and, in benign disease, to describe the presence, or absence, of dysplasia.

Oral proliferative verrucous leukoplakia has a different appearance of the white plaques, and it is a rare, aggressive form of leukoplakia with a higher risk of malignant transformation. The lesion is multifocal and exophytic, presenting with a wartlike appearance. Unlike oral leukoplakia, this disorder is more common in elderly women across all ethnic groups; an association with tobacco or alcohol use and human papillomavirus has not been established. Pathologic features differentiating oral proliferative verrucous leukoplakia from oral leukoplakia and other lesions of the tongue include a dense lichenoid inflammatory process, including basal vacuolar degeneration, apoptotic cells, eosinophilic bodies, and a bandlike lymphocytic infiltrate, with an exophytic warty configuration.

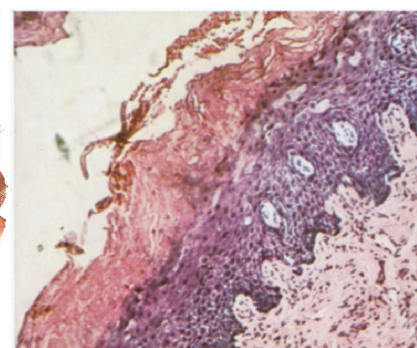
Oral hairy leukoplakia is one of the most common oral manifestations of HIV infection, believed to be due to infection caused by the *Epstein-Barr virus*. It presents most often as a white thickening of the lateral border of the tongue with vertical hairlike projections and corrugations. Although it can extend to the ventral and dorsal surfaces of the tongue, it is rarely seen in other parts of the oral cavity. Unlike oral leukoplakia or oral proliferative verrucous leukoplakia, there is no risk of malignant transformation.

Leukoplakia of the cheek is usually found parallel to the line of occlusion, sometimes extending from the corners of the mouth as a pattern of fanlike radiating lines.

A favorite site of leukoplakia is the lower lip, where a barely discernible whitish plaque (smoker's patch)

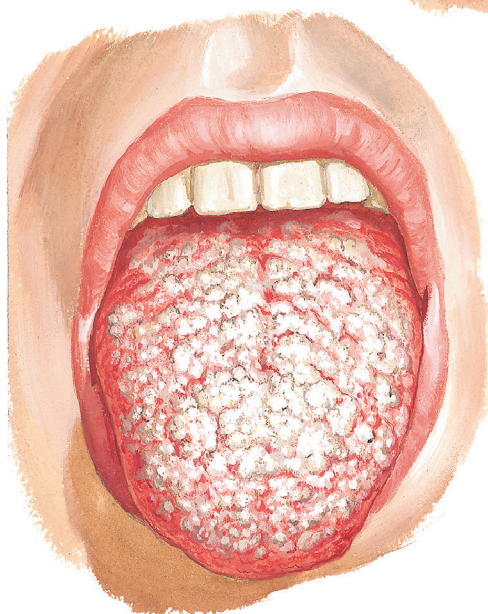
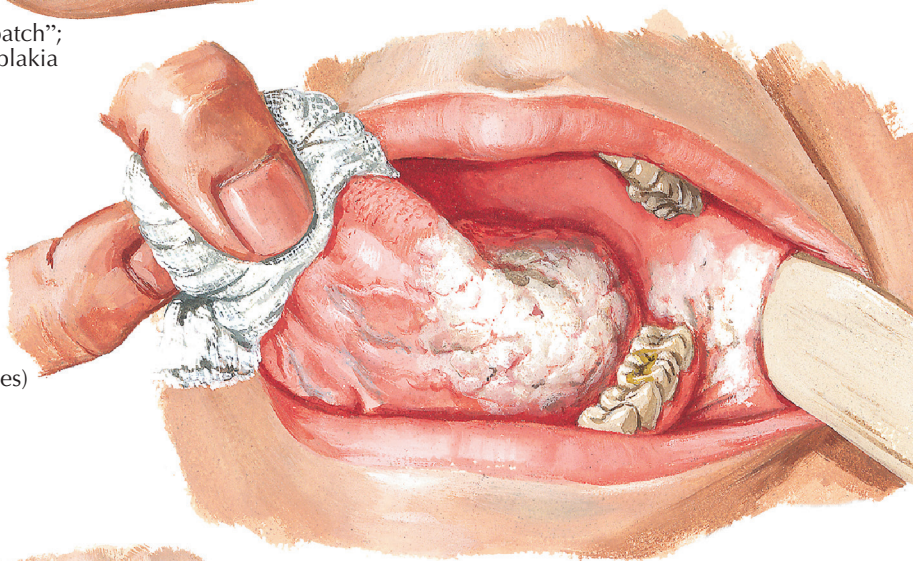


"Smoker's patch";
early leukoplakia

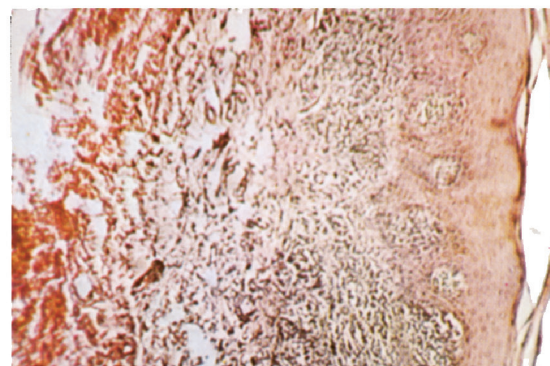


Leukoplakia with beginning dyskeratosis

Moderately
advanced
leukoplakia
of tongue
and cheek
(raised plaques)



Advanced leukoplakia of tongue



Lichen planus

appears, which at first may be removed by rubbing but becomes more permanent and thickened with time. *Leukoplakia of the palate* may manifest as a diffuse grayish white discoloration or as discrete plaques or rings around the orifices of the palatal mucous glands, which, in time, may become enlarged and nodular, owing to chronic obstruction.

The diagnosis of leukoplakia requires differentiation from syphilis, thrush, carcinoma, lichen planus, and traumatic scars.

Lichen planus presents a very similar picture, although the delicacy of the lacy markings, the skin lesions, and its presence in women help to identify it and distinguish it from leukoplakia. A biopsy is most indicative although not always definitive. The histologic features of leukoplakia, including hyperkeratosis, accentuation of the stratum granulosum, and moderate dyskeratosis of the prickle cells with hyperchromatic nuclei, particularly in the cells of the basal layer, differentiate it from lichen planus.

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EFFECTS OF IATROGENIC AGENTS ON ORAL MUCOSA

Traumatic ulcers occur from acute or chronic injury to the lips, tongue, or cheek from biting the tongue or cheek or lacerating the mucosa with sharp objects or broken dentition. The ulcers are often painful and characterized by mild erythema surrounded by a central ulcer covered by a yellow fibrinopurulent membrane.

Injury from caustic chemicals varies with the degree of concentration of the agent and the duration of contact time with the mucosa, from no injury to severe ulceration.

An *aspirin burn* can result from residual acetylsalicylic acid from chewing an aspirin or from topically applied solutions. This can produce a surface necrosis with blebs, which later sloughs, leaving superficial erosion. The onset is rapid, as is healing. Use of hydrogen peroxide to treat oral conditions can result in epithelial necrosis when left in contact with the oral mucosa for too long or with concentrations that exceed 1% to 3%. Similarly, phenol or silver nitrate, both of which are used to treat aphthous ulcerations, can damage the mucosa and associated nerve endings.

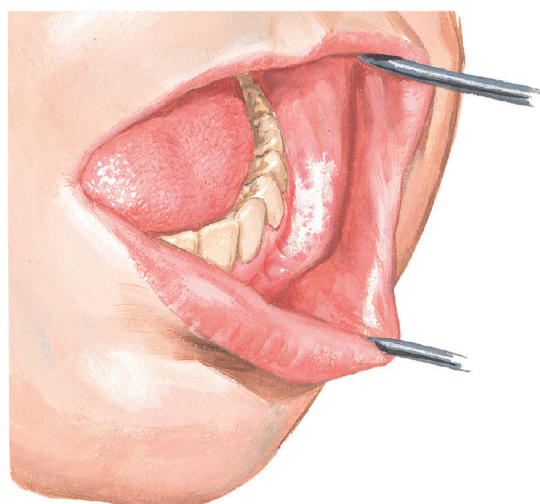
Nicotine stomatitis presents as slightly raised, white papular lesions on the posterior aspect of the hard and soft palates, primarily in association with pipe or cigar smoking. The central portions of the papules have a reddish component resulting from inflammation of the minor salivary gland duct orifices.

Intensive chemotherapy and radiation therapy to the head and neck region frequently causes painful stomatitis, which can limit the dosage and frequency of the therapeutic regimens and interfere with oral intake. Inhibition of cell growth and maturation by these agents disrupts the mucosal barrier, allowing for opportunistic infections by otherwise normal oral microflora. Salivary glands can be affected as well, resulting in xerostomia, which further increases the vulnerability of the oral mucosa.

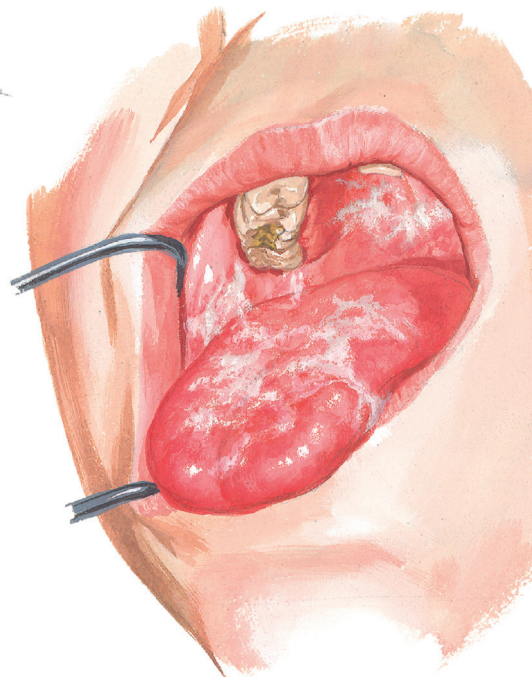
Stomatitis can be seen with less noxious ingestions than the neoplastic agents.

Wide-spectrum antibiotic use results in an imbalance of the endogenous flora, causing a secondary infection from *Candida albicans*. Pseudomembranous candidiasis or oral thrush is the most common presentation; it is characterized by multiple white creamy curdlike plaques located anywhere in the oral cavity.

The pale bluish-to-heavy-black *lead line* (Burton line or halo saturninus), along the gingival margin, is a symptom of lead absorption but not necessarily of lead intoxication. The primary cause of toxicity is the binding of lead with sulfhydryl groups competing with enzymes that use the binding site. Additionally it



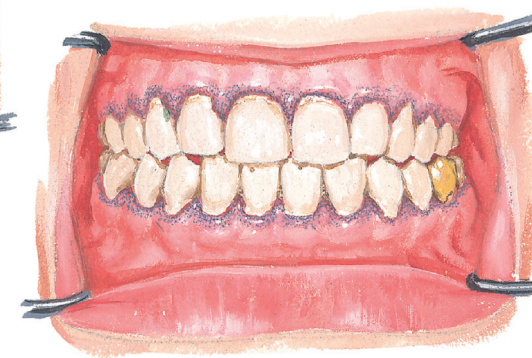
Aspirin burn



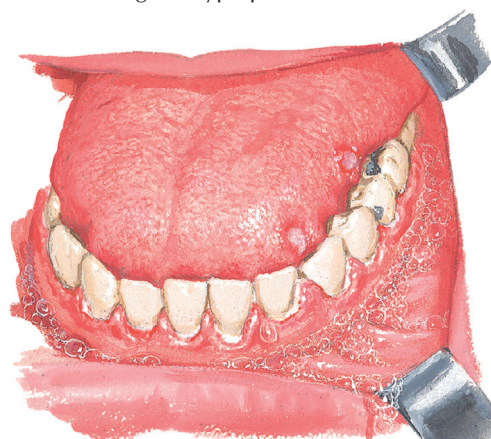
Stomatitis and glossitis developing during antibiotic therapy



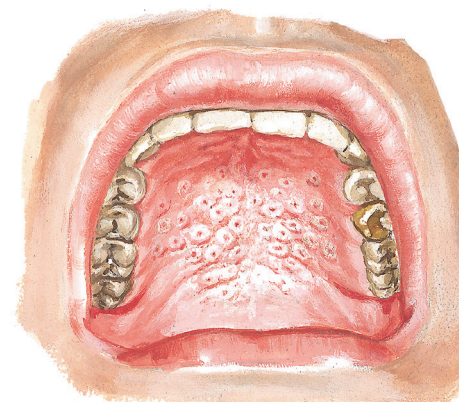
Gingival hyperplasia due to Dilantin



Lead line (halo saturninus)



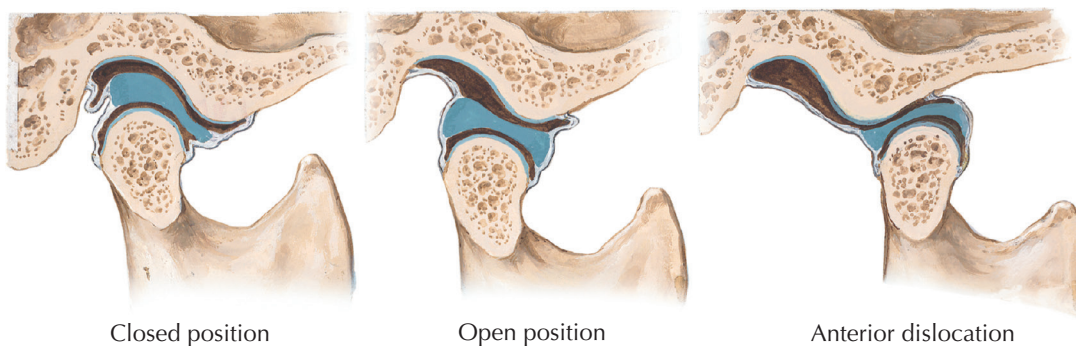
Mercurialism



Stomatitis nicotina

mimics metals such as calcium, iron, and zinc, which are needed cofactors in many enzymatic reactions. The lead line consists of lead sulfide that has precipitated in the capillaries or surrounding tissue, when the lead compounds circulating in the blood react with hydrogen sulfide. The latter is liberated by bacterial action from organic matter deposited around the teeth as a consequence of poor oral hygiene. Secondary invasion of fusiform and spirochetal organisms often occurs, producing a marked gingivitis.

Gingival hyperplasia is a complication of the anticonvulsive drug phenytoin. Edentulous mouths do not reveal the disturbance, emphasizing the role of local irritants and oral hygiene. All gradations of hyperplasia are observed, beginning with tumescence of the interdental papillae. The consistency is fibrotic, without edema, inflammation, or color change. The swellings may further proliferate to cover the crowns of the teeth with sessile, lobulated growths that are light pink in color and sharply defined from the surrounding gum.



Closed position

Open position

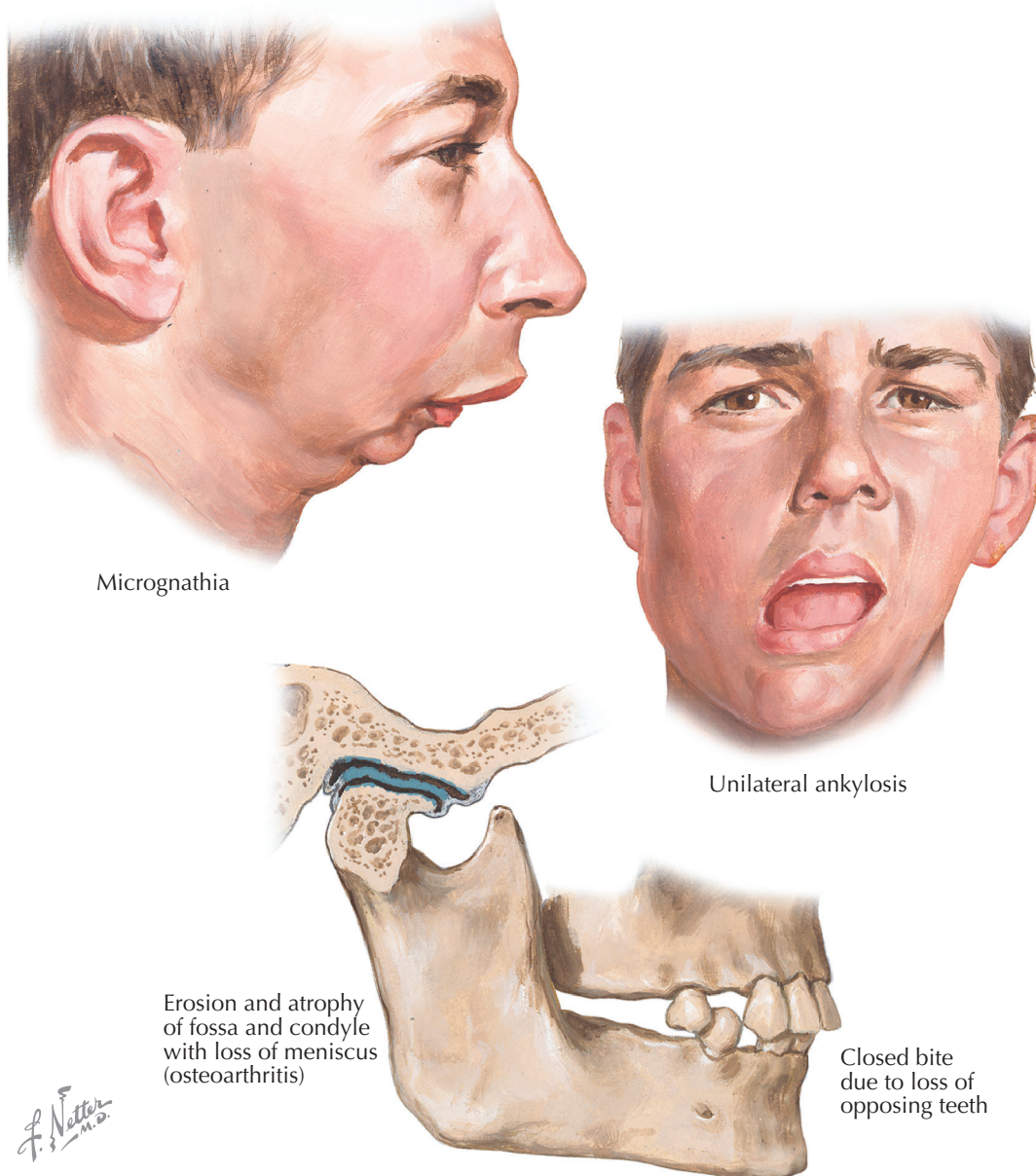
Anterior dislocation

ABNORMALITIES OF TEMPOROMANDIBULAR JOINT

The glenoid fossa of the temporal bone and the mandibular condyle constitute a compound, diarthrodial joint, separated by an articular cartilage and enclosed by a synovial membrane and capsular ligament. The upper compartment (meniscotemporal articulation) permits gliding motions, and the lower compartment (meniscocondylar articulation) functions as a hinge. Muscle action and the occlusal relations of the teeth are the major determining factors in movements of the joint, with the anatomy of the bony surfaces and the articular ligaments less important than in other joints.

Facial height and form depend largely on the proper growth of the mandible. Whereas the maxilla grows by apposition against the anterior base of the cranium, the mandible develops vertically by an epiphyseal type of growth from the head of the condyle. Interference with the chondrogenic zone of the condyle has a disastrous effect on the facial profile. Growth arrest, partial or complete, may be the result of otitis media, radiation, arthritis, condylar fracture, or trauma by obstetric forceps. Complete arrest of mandibular growth or ankylosis occurring during childhood gives rise to *micrognathia*, a deformity in which the condylod process is shortened, with an obtuse mandibular angle, a stunted mental protuberance, and a concave lower border of the bone resulting from the powerful action of the depressor muscles. *Dislocation of the condyle* may ensue from a blow on the ramus or chin when the mouth is open, from yawning, or from excessive manipulation of the jaw under general anesthesia. The dislocation is nearly always forward, the condyle resting anterior to the articular eminence. Backward displacement occurs rarely from a forceful blow, at the expense of the posterior attachment of the meniscus. The condyle then rests on the bony surface of the fossa, with a slight tilting of the mandible and an open position of the anterior teeth. Other dislocations are seen only with fractures of the condyle or base of the skull. Chronic injury to the joint ligaments as, for example, by malocclusion of the teeth may lead to subluxation. A hypermobility of the condyle is accompanied by a clicking or snapping sound at the termination of opening. This sound is due to the condyle's slipping anteriorly past the meniscus and then striking the articular eminence. The same action occurs when the attachment of the external pterygoid muscle to the capsule has been lost through injury.

Fracture of the condyle is seen frequently as a result of a frontal blow on the chin. Displacement of the condylar head is sometimes caused by the trauma itself; more commonly, it is caused by the pull of the external



Micrognathia

Unilateral ankylosis

Erosion and atrophy of fossa and condyle with loss of meniscus (osteoarthritis)

Closed bite due to loss of opposing teeth

pterygoid muscle inward and forward. Following bilateral fracture of the condylar necks, the molar teeth close prematurely but the incisors are still separated.

Ankylosis may result from injury or inflammation of the joint. Occasionally, extraarticular causes, such as fibrosis and cicatrization of the muscles attached to the mandible, cause a false ankylosis. This may happen in healing of extensive wounds of the face and in post-radiation cases of head and neck cancer. In ankylosis proper, the cause can be a comminuted fracture of the

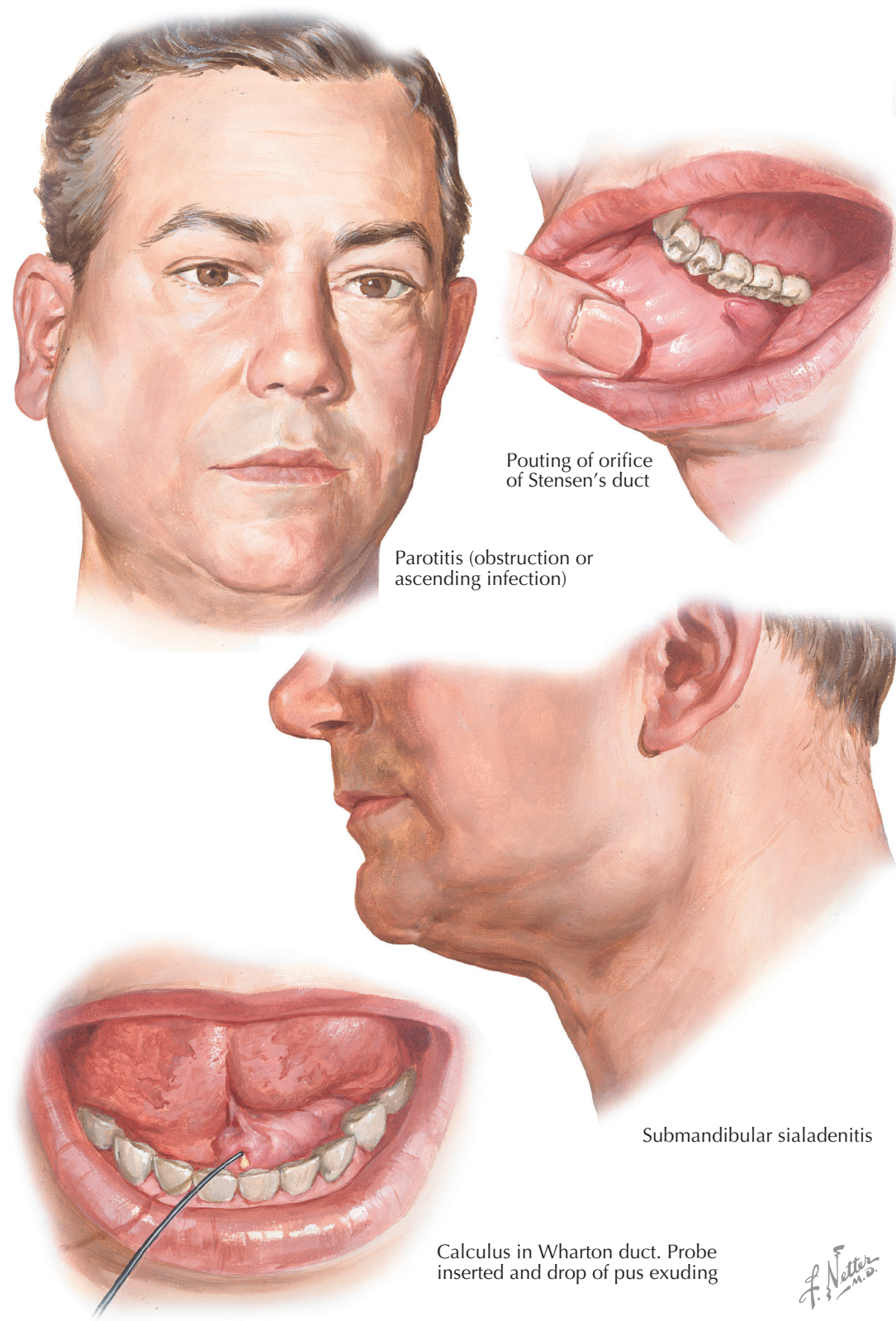
condyle, suppurative arthritis or osteomyelitis, intracapsular hemorrhage, or rheumatoid arthritis. The ankylosis may be fibrous, with perceptible but slight movement, or bony. *Unilateral ankylosis* is characterized by a marked limitation of movement and a deviation toward the affected side on opening of the mandible. The uninjured condyle describes an arc about the injured condyle, which acts as a fulcrum. Muscles on the normal side hypertrophy; on the injured side, they atrophy.

INFLAMMATION OF SALIVARY GLANDS

The major salivary glands and the accessory mucous glands are subject to functional abnormalities as well as inflammation. *Amylase mia* (*ptyalism*), or excessive salivation, is associated with the use of several drugs, specifically, clozapine, pilocarpine, and risperidone. Toxins such as mercury, copper, and organophosphates have also been reported to cause excessive salivation. Most often, however, excessive salivation is caused by a form of gastroesophageal reflux known as *water brash*. On the other hand, *xerostomia*, or dryness of the mouth, most often results from frequently used medications such as anticholinergic agents, radiation to the head and neck, chemotherapeutic treatment, obstructive sleep apnea, and, less often, Sjögren syndrome, vitamin deficiencies, and other systemic conditions. Inflammation of the major glands is usually shown by swelling and may be a feature of a generalized syndrome. Epidemic parotitis or Hodgkin or leukemic infiltration should be considered diagnostically whenever more than one gland is involved or when a local cause is not obvious.

The *submandibular gland* may be the site of an acute or subacute infection, causing pain on palpation. The swelling differs from that of an alveolar abscess by being deeply seated, not complicated by trismus, and presenting as subepithelial nonadherent swelling beneath the mandible with distinct borders. The orifice of the Wharton duct is reddened, and its course is tender and edematous. Pus may sometimes be expressed by milking the duct. Swelling of the submandibular gland is most often due to obstruction in the form of a salivary calculus. Precipitation of calcium salts is probably initiated by irritation of the duct and stasis of saliva, aided by the presence of a matrix of filamentous colonies of saprophytic *Actinomyces* or other organisms.

The *parotid gland* is subject to similar acute and chronic swellings superimposed on recurrent obstruction of its duct. It may also become infected by an ascending pyogenic infection of the Stensen duct in debilitated or postoperative patients. In this "terminal parotitis," the onset is sudden, with severe pain, fever, and swelling of the parotid gland. Obstructive parotitis, in contrast to submandibular adenitis, is usually not associated with calculus formation. An inflammatory disturbance in the duct or catarrhal constriction causes characteristic recurrent swelling. Complete obstruction predisposes to abscess formation, with reddening of the



skin and a tense, fluctuant swelling of the parotid space. Repeated parotitis may lead to stenosis of the interlobar ducts or main excretory duct.

Mumps, a highly contagious viral infection causing parotid gland swelling, usually affects both glands, which have a doughy or elastic consistency. The frequency of this infection had diminished after immunization became available for young children, but now that parents are becoming more resistant to immuniza-

tions, the frequency is again increasing. The glands enlarge to the maximum size within 24 to 48 hours and remain enlarged for 7 to 10 days. Microscopically, the glands are heavily infiltrated by lymphocytes and show destruction of acinar cells in varying degrees. The danger of mumps lies in the complications, which include epididymo-orchitis, oophoritis, meningo-encephalitis, deafness, ocular lesions, and neuritis of the facial and trigeminal nerves.

ORAL MANIFESTATIONS IN SYSTEMIC INFECTIONS

Oral manifestations can be observed in almost every generalized systemic infectious disease. Only the most characteristic ones are illustrated on this page.

Measles produces a pathognomonic eruption of the mouth in the prodromal stage before any cutaneous lesions have become evident. About the second day after the first signs of the disease (coryza, conjunctivitis, and fever) become evident, the palate and fauces become intensely red, and the typical *Koplik spots* appear on the buccal or labial mucous membranes as isolated rose-red spots with a pale bluish white center. At the onset, the buccal mucosa is normal in color. Soon the eruptions become diffuse, with rose red predominating and the bluish spots more numerous, until the coalescence of all spots produces an even redness, with myriad white specks. The cutaneous rash, which is dull red and macular, follows the first Koplik spots by 2 to 3 days. The oral mucosa assumes its normal color before the skin rash has disappeared.

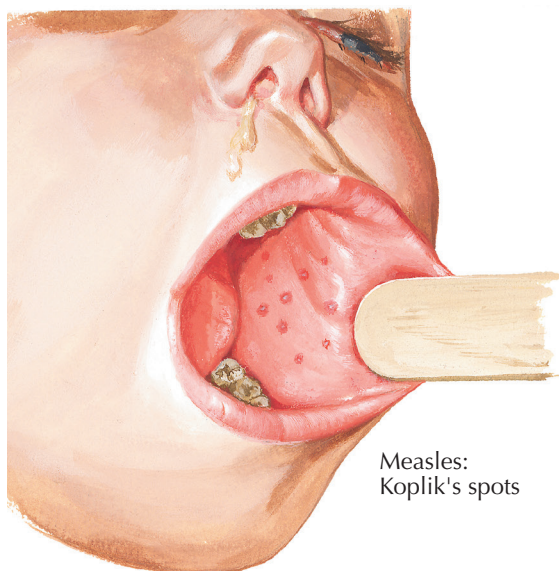
The vesicular eruptions of *chickenpox* may be seen in the oral cavity before the skin eruptions appear, and they are mainly seen as isolated small vesicles on the soft palate. The thin vesicles, with a reddened halo, rupture quickly to form shallow erosions with gray tags of epithelial debris. Usually, the size is that of a pinhead, but it may be larger. It resembles a solitary aphtha but is generally not as painful.

The oral symptoms of *scarlet fever* originate in the throat, which is red and swollen, as are the tonsils and palate and, occasionally, the gingivae. The tongue is next involved with a heavy, grayish, furry coating through which enlarged, red papillae are scattered. The edges of the tongue and its tip are vividly red. Within 3 or 4 days the dorsum has desquamated, with enlarged variously placed papillae, presenting the so-called strawberry tongue.

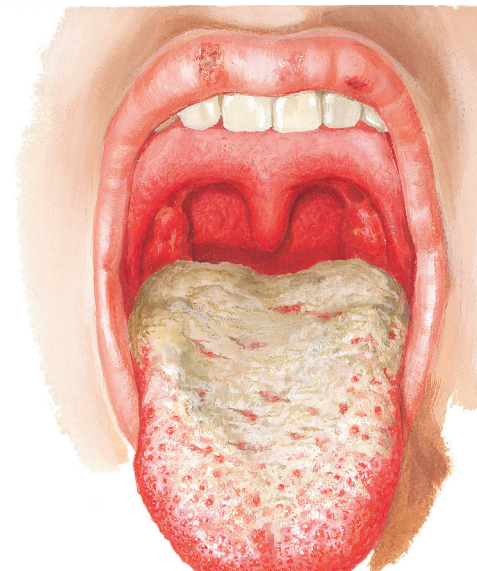
Foot-and-mouth disease, or epizootic stomatitis, is an acute, highly contagious viral infection that can be transmitted to humans by the consumption of unsterilized milk or meat from cows suffering from the disease or by direct contact with the saliva of infected animals. The oral symptoms follow generalized fever and malaise with dry, swollen, reddened membranes. The tongue is coated and enlarged. Within days, yellow vesicles appear and rupture. Salivation and a fetid odor are prominent. The vesicles enlarge and then appear also on the hands and, occasionally, the toes. Fever and lymphadenopathy increase for 1 to 2 weeks, after which time they rapidly resolve.

Infectious mononucleosis presents as a triad of fever, tonsillary pharyngitis, and lymphadenopathy as a result of infection with the *Epstein-Barr virus* between intimate contacts. In the early stage, usually with the onset of the fever, a reddened pharynx is seen with scattered petechiae of the buccal and labial mucosa and of the soft palate. The presence of palatal petechiae, splenomegaly, and cervical lymphadenopathy is highly suggestive of the infection. A heterophile antibody agglutination test (Paul-Bunnell reaction, sheep red blood cells; monospot, horse red blood cells) will establish the diagnosis.

The primary lesion of *sypilis* is the *chancre*; 5% to 10% of lesions are extragenital, often around the oral cavity. Lip chancre is typically a sole lesion, the erosive



Measles:
Koplik's spots



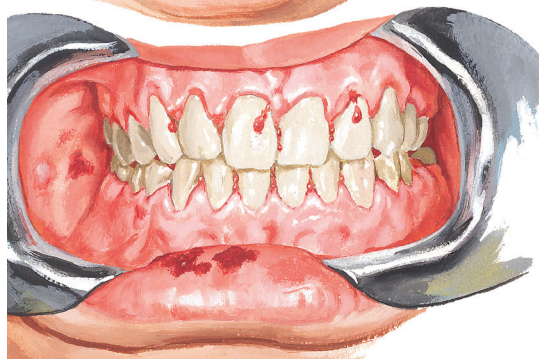
Scarlet fever
(entire tongue later assumes strawberry characteristics illustrated here at tip)



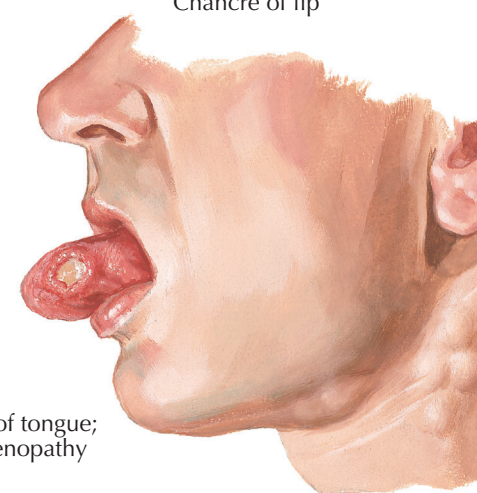
Foot-and-mouth disease



Chancre of lip



Infectious mononucleosis



Chancre of tongue;
lymphadenopathy

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type resembling a herpetic lesion with a tendency to crust and ooze. Lymphadenopathy is present and is unilateral, hard, movable, and slightly tender. The chancre contains numerous spirochetes. Chancre of the tongue presents as a circular lesion surrounded by indurated raised reddened tissue on the tongue tip; however, less typical chancres can develop on the gingiva, buccal mucosa, palate, and tonsils. By 4 to 6 weeks from the appearance of the chancre, the oral infection increases

to include mucous patches on the tongue, buccal mucosa, pharynx, and lips, which contain numerous *Treponema* organisms. The tongue often has multiple gummas in the form of pea-size nodules on the dorsum. Ulceration and necrosis heal with stellate and grooved scars typical of leucic interstitial glossitis, or they may be extensive, causing macroglossia. Treatment with a penicillin-based antibiotic is very effective at the primary stage of the disease.

ORAL MANIFESTATIONS OF GASTROINTESTINAL DISEASES

Inflammatory bowel diseases (IBDs), most notably Crohn disease and ulcerative colitis, are primary intestinal diseases. Both main forms demonstrate a spectrum of oral lesions. These manifestations may be the initial presentation of the disease, and the course of the lesions may be dependent on or independent of bowel disease activity. The incidence of oral lesions in IBD is estimated to be 20% to 50%; lesions are most commonly seen in children with Crohn disease. Oral lesions specific to Crohn disease are histopathologically granulomatous and typically visualized on the buccal mucosa, gingiva, lips, and vestibular and retromolar areas. Four oral lesions specific to Crohn disease have been described: (1) White reticular tags, seen most frequently in the labial, buccal, and retromolar regions, form non-caseating granulomas, referred to as *indurated taglike lesions*. (2) *Cobblestoning* of the buccal mucosa, most often in the posterior region, is created by hyperplasia and fissuring of the mucosa, primarily in the posterior buccal region and palate; the fissuring results from the formation of mucosa-colored papules that degenerate into firm painful plaques. (3) *Mucogingivitis* is an edematous, granular, hyperplastic gingiva without ulcerations. (4) *Lip swelling* occurs, with vertical fissures, deep linear ulcerations in the buccal sulci, and midline labial fissuring. None of these oral lesions vary with disease activity. All can be treated with immunosuppressive medications; topical drugs are most often used, but systemic drugs can be used if disease is severe.

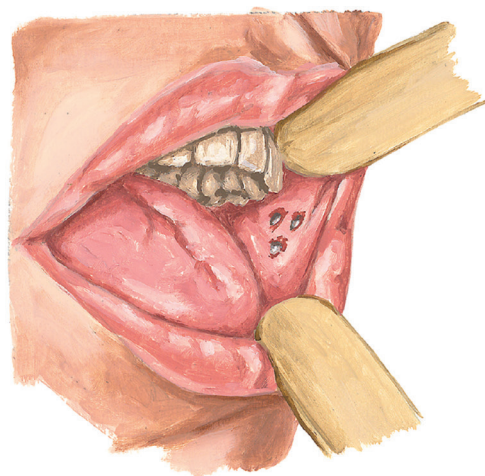
Nonspecific oral lesions can be seen in IBD patients, as well as in the general population. *Aphthous stomatitis* is seen in IBD patients, with greater frequency in rheumatologic patients and lesser frequency in the general population. The lesions are round, shallow ulcerations with fibrinous exudate and an erythematous border.

Pyostomatitis vegetans, a chronic mucocutaneous ulcerative condition, presents with multiple milium white or yellow pustules surrounded by an erythematous, edematous mucosal base; it is most often visible in the labial, gingival, and buccal mucosa. The pustules rupture and coalesce to form a linear, or snail track, ulceration. This type of ulceration has also been described in secondary syphilis. These lesions are non-specific to IBD, but when they are associated with IBD, the type of disease is most frequently ulcerative colitis.

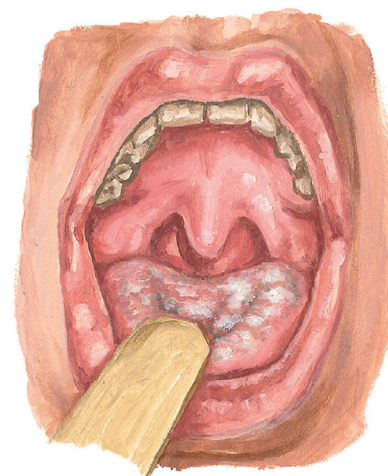
Gastroesophageal reflux disease (GERD) results from movement of the gastric contents cephalad, traversing the lower esophageal sphincter, esophagus, and upper esophageal sphincter and moving into the oral cavity. *Dental erosions*, specifically those occurring on the lingual and palatal surfaces of the teeth, are complications of this condition. Acid is the likely corrosive agent in this process. The critical pH for demineralization is 5.5, but it varies inversely with the concentration of calcium and phosphate in saliva. Several studies have indicated that *halitosis* could be considered an extraesophageal manifestation of GERD. The etiology of this relationship is less clear but is likely explained physiologically by the degradation of anaerobic bacteria of sulfur-containing amino acids.

Peutz-Jeghers syndrome is an autosomal dominant disease characterized by multiple gastrointestinal tract hamartomatous polyps and *mucocutaneous pigmentation*. The pigmentation is due to macrophage-filled melanin-pigmented, flat blue-gray or brown spots of 1 to 5 mm located in the dermis of the lips and buccal region. The diagnosis can be made by histologic examination of one

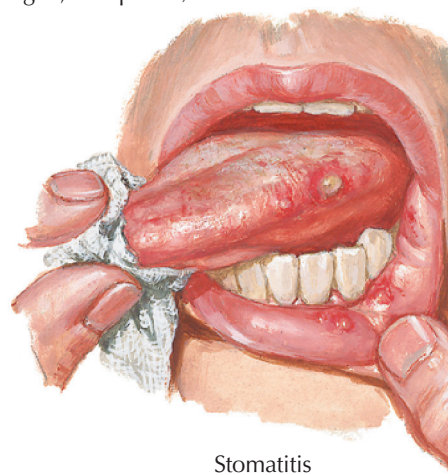
Oral ulcers



Aphthous ulcers (occur on buccal mucosa, tongue, and palate)



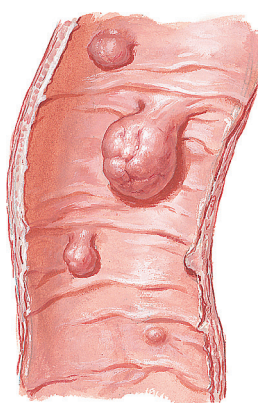
Oral candidiasis (secondary to chronic illness and use of antibiotics)



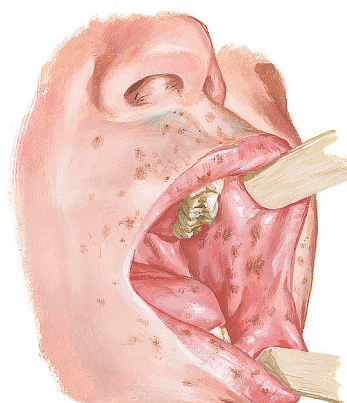
Stomatitis

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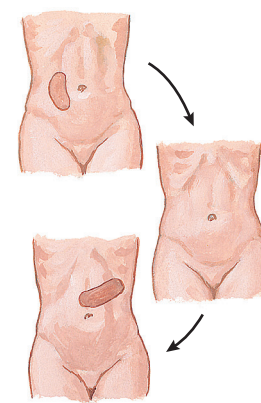
Peutz-Jeghers syndrome



Polyposis of small intestine



Mucocutaneous pigmentation



Intermittent, migrating mass (due to self-reducing intussusception)

of the luminal polyps in an index case or by gross identification of the polyps or noting the presence of mucocutaneous pigmented lesions in an individual who has a first-degree relative in whom the disease was previously diagnosed.

Gardner syndrome is an autosomal dominant disorder characterized by colorectal polyps and extracolonic tumors. Similar to familial adenomatous polyposis (FAP), the genetic mutation responsible for the disease is the adenomatous polyposis gene. The risk of malig-

nant transformation of the colorectal polyps is significant. Unlike FAP, Gardner syndrome is characterized by the presence of multiple osteomas, epidermoid cysts, desmoid tumors, and cutaneous fibromas. The osteomas most often develop in the maxilla and mandible. Dental abnormalities can be seen in about 30% of patients even in the absence of osteomas. The abnormalities seen include supernumerary teeth, compound odontomas, hypodontia, abnormal tooth morphology, and multiple impacted teeth.

ORAL MANIFESTATIONS OF RHEUMATIC DISEASES

Oral abnormalities seen in rheumatologic disease are secondary to the pathophysiology of the disease process and result from the medications used to treat the disease. The oral manifestations of *Sjögren disease* can cause an exacerbation of the underlying illness and alter an individual's quality of life. At the core of this problem is an alteration in salivary production and flow. An infiltration of lymphocytes into the salivary gland results in irreversible damage to the gland and decreased or absent saliva production.

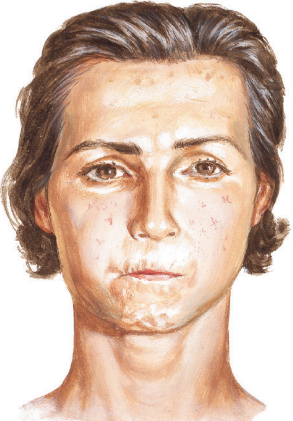
Xerostomia, commonly known as dry mouth, results from the inability of the salivary glands to produce saliva following destruction or atrophy of the glands and is paramount in Sjögren disease. Saliva is critical to the maintenance of oral health; therefore, its absence results in mastication difficulties, increased dental caries, and oral infections. Changes in the diet to reduce acidity, avoid foods containing sugar, and increase noncaloric clear fluid irrigation may reduce the effects of a low-saliva state. Pharmacologic interventions including cevimeline or pilocarpine are somewhat effective in the stimulation of saliva production.

Decreased (*hypogeusia*) or disordered (*dysgeusia*) taste may be a consequence of xerostomia that further complicates Sjögren disease.

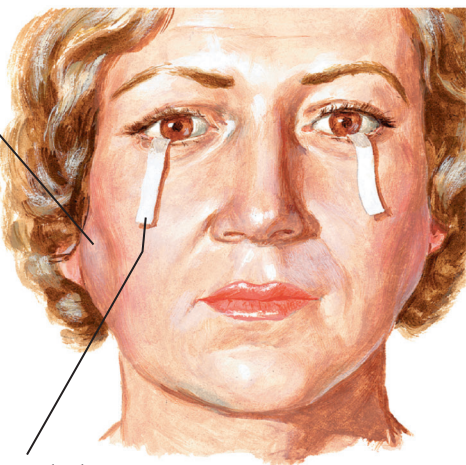
Systemic sclerosis is a progressive autoimmune connective tissue disease resulting in vascular damage and tissue fibrosis. Fibrosis of the salivary gland in the absence of inflammation results in the same salivary alterations seen with Sjögren syndrome. Immunosuppressive agents used to treat these diseases can result in an increase in oral infections such as candidiasis. In addition to the decreased saliva production, diminished interincisal distance, increased tooth loss, and periodontal disease are seen in progressive systemic sclerosis. Limitation of mouth opening is likely a result of periorbital tissue fibrosis, and changes in interincisal distance are complications of progressive systemic sclerosis.

Behçet syndrome is a systemic vasculitis of unknown etiology characterized by a triad of recurrent oral *aphthous ulcers*, genital ulcers, and uveitis. The mucocutaneous lesions are the hallmark of the disease, with oral ulcers occurring in 97% to 99% of patients. The oral lesions are visibly indistinguishable from canker sores, but they occur in multiples and recur frequently. They are small, ovoid lesions with circumscribed margins and a yellow-gray base frequently surrounded by a rim of erythema. *Minor aphthous ulcers* are the most frequent oral lesion in Behçet syndrome; they are typically

Progressive systemic sclerosis



Sjögren syndrome



Parotid gland swelling

Schirmer test
Strips of filter paper inserted behind lower lids. Wetting of 15 mm or more of strip outside of lid = normal; <5 mm = definitely abnormal; 5-15 mm = probably abnormal

Systemic Lupus Erythematosus



Malar rash

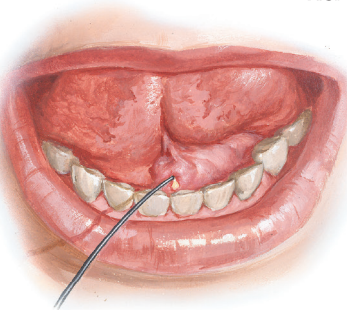


Painless oral ulcers



Livedo reticularis

Xerostomia

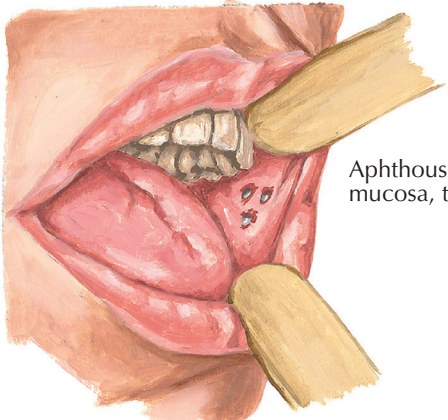


Calculus in Wharton duct. Probe inserted and drop of pus exuding



Xerostomia and glossitis

Behçet disease



Aphthous ulcers (occur on buccal mucosa, tongue, and palate)

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smaller, under a centimeter in diameter, and usually heal without scarring. In contrast to the major herpetiform ulcers that typically form scars following healing, the aphthous ulcers are most often seen on nonkeratinized mucosal surfaces, such as the labial and buccal mucosa and the floor of the mouth. Herpetiform ulcers are multiple and much smaller, usually 2 to 3 mm in diameter; however, they can coalesce to form a larger ulcer. They differ from herpetic ulcers by not being preceded by vesicles and by not containing viral particles.

Disseminated lupus erythematosus is a chronic inflammatory disease of unknown etiology that can affect any organ system. Oral lesions are present in about 15% of cases and consist of irregular red patches, which may become eroded, atrophic, and, later, scarred. White pinhead spots are discernible about the periphery. The sites of predilection are the cheeks, palate, and lips.

ORAL MANIFESTATIONS RELATED TO ENDOCRINE SYSTEM

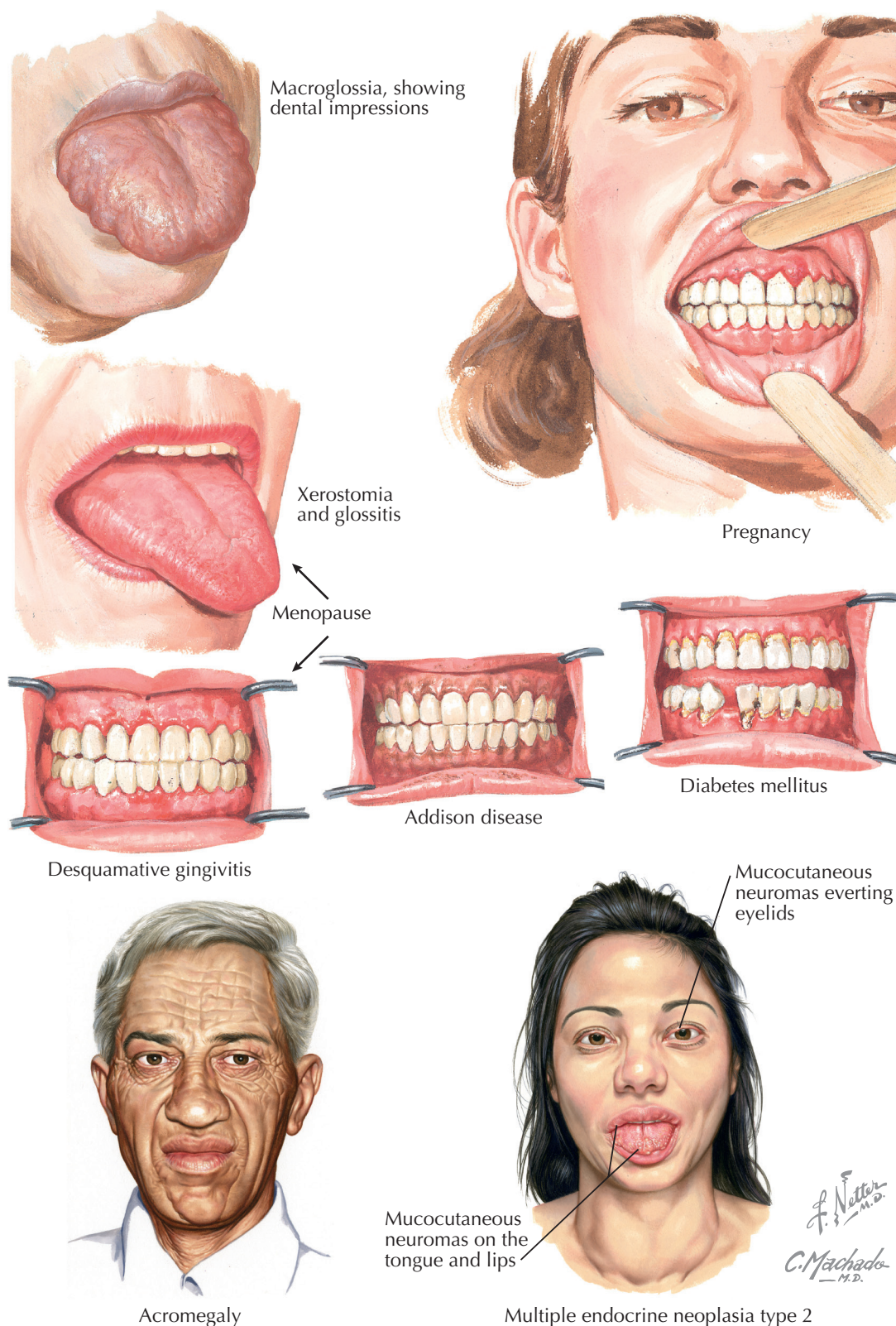
The gingivae and tongue frequently exhibit changes during times of hormonal fluctuations. Marginal gingivitis characterized by hyperemia producing a deep raspberry color of the gum margin, associated with hyperplasia in the interdental papillae, is not uncommon during menstruation. Poor oral hygiene resulting in increased debris is often a contributing cause.

In *pregnancy*, a chronic marginal gingivitis is fairly common, beginning in the second month and often continuing after delivery. Symptoms range from slight hyperplasia and bleeding to mulberry-like swellings or fungoid proliferations, frequently called the pregnancy tumor. Fibrous epulides occurring prior to pregnancy are markedly stimulated in growth. Clinically, the gum shows proliferation of a granulation type of tissue, which appears edematous and turgid. Histologically, there is hydropic degeneration of the epithelium, loss of keratin, and proliferation of rete pegs, with infiltration and fibrinous exudate in the corium.

Menopause is often accompanied by alterations in taste and burning, dryness, and soreness of the oral mucosa, especially of the tongue. Objective signs include papillary flattening, fusion, and glazing, similar to vitamin B deficiency states, occasionally resembling the acute redness and pebbly appearance of the mild pellagrous tongue. A special form of *desquamative gingivitis* is sometimes associated with menopause, causing recurrent denudation of the gingivae or buccal mucosa, which may be painful.

Increased pigmentation of the skin and mucosal membranes is an early sign of *Addison disease*. This pigmentation is caused by a deposition of melanin; it appears only in chronic primary deficiency of the adrenal cortex and is not a result of insufficiency from pituitary dysfunction. In the oral cavity, melanin may be deposited in the mucosa of the lips, cheek, and tongue and along the gingivae. The color of the pigmentation varies from a pale brown to a dark blue, depending on the severity of the disease. Though produced by other mechanisms, increased deposits of dark pigments along the oral mucosa occur in other conditions, such as hemochromatosis, malaria, liver cirrhosis, alkaptonuria, and argyrosis.

Diabetes mellitus, in a controlled state, seldom produces characteristic lesions of the mouth. Mucosal findings in poorly controlled diabetes may present as deeply reddened and dry, with an abundance of calcareous deposits and soft detritus around the teeth. Pronounced gingival recession, periodontal bone loss, ulceration, and loosening of teeth are other associated phenomena. *Acromegaly* is caused by an excess of growth hormone secretion, resulting in coarsening facial features and soft tissue swelling of the hands and feet. *Prognathism*, or protrusion of the jaw, is a consequence of overgrowth of the mandible. Additionally, oral features seen in acromegaly include macroglossia, malocclusion of the teeth, and widening of the dentition.



Multiple oral findings are seen in children with *hypothyroidism*, including macroglossia caused by an edematous infiltrate, edematous lips, and malocclusion. The deciduous teeth are retained beyond the normal shedding time, resulting in a delay in tooth eruption.

Multiple endocrine neoplasia (MEN) is a term encompassing several distinct syndromes each of which involves endocrine gland tumors. *Mucosal neuromas* are a part of MENIIB (sometimes referred to as MEN 3),

which also includes medullary thyroid cancer, pheochromocytoma, and a marfanoid body habitus. The mucosal neuromas are multiple asymptomatic, soft painless papules or nodules that are most often present on the lips and tongue but can also be found on the buccal mucosa, gingiva, and palate. The lesions consist of hyperplastic bundles of nerves surrounded by thickened perineurium situated within a normal submucosal connective tissue stroma.

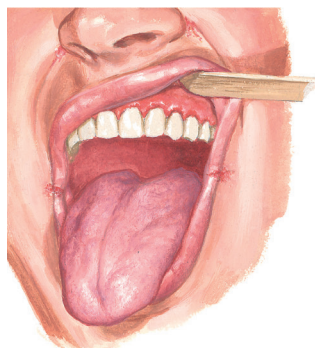
ORAL MANIFESTATIONS IN NUTRITIONAL DEFICIENCIES

The oral mucous membranes are exquisitely sensitive to nutritional deprivation; however, pathognomonic findings are seen in very few deficiency states. Clinically significant malnutrition has multiple causes, including dietary insufficiency, decreased absorption, and increased elimination or metabolic demand. *Ariboflavinosis*, as a clinical syndrome, presents with specific features that can be attributed to riboflavin deficiency. The oral lesions in ariboflavinosis begin with pallor of the labial mucosa and the skin at the corner of the mouth, followed by maceration of the epithelium and the formation of fissures and crusts. The angular and vertical fissures and superficial ulcerations are termed *cheilosis*; they are seen at the corners of the lips and along the lips and mucous membranes. Loss of differentiation along the mucocutaneous border is typically seen in a deficiency of riboflavin. The association of conjunctivitis, corneal opacities and increased vascularization, photophobia and signs of dermatitis in the nasolabial regions, together with cheilosis, may be considered pathognomonic for ariboflavinosis, particularly so if signs of glossitis can be observed simultaneously. Although not a universal finding, the most striking features on the tongue are a purplish magenta discoloration and a pebbly appearance resulting from early edematous enlargement of the fungiform papillae. Atrophy of the filiform papillae is not limited to riboflavin deficiency but rather may extend to B complex deficiency. Ariboflavinosis is not restricted to tongue manifestations; the gingivae may be colored more deeply red than is normally seen in nondeficient states.

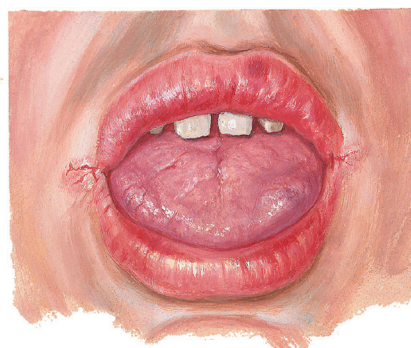
Deficiencies in *niacin* and *pyridoxine* can result in a scalding sensation of the tongue, which is followed by reddening and hypertrophy of filiform papillae; it can ultimately produce a bald lingual surface that is beefy red in color.

Pellagra is presently thought to be a disease caused by lack of several vitamins of the B group but primarily of nicotinic acid and the essential amino acid tryptophan. Soreness of the tongue and mouth may be one of the initial signs, but the fully developed changes of pellagrous tongue appear at a later stage. The papillae of the lateral margins and tip are first affected, and the changes progress to involve the entire tongue and all mucous membranes. The color at this time is scarlet red. Increased soreness and salivation are accompanied by edema, with indentations from the teeth and, often, ulcerations. Later, the tongue becomes bald and more beefy red in color. The papillary changes involve, first, hypertrophy, flattening, and coalescence (producing furrows) and then atrophy.

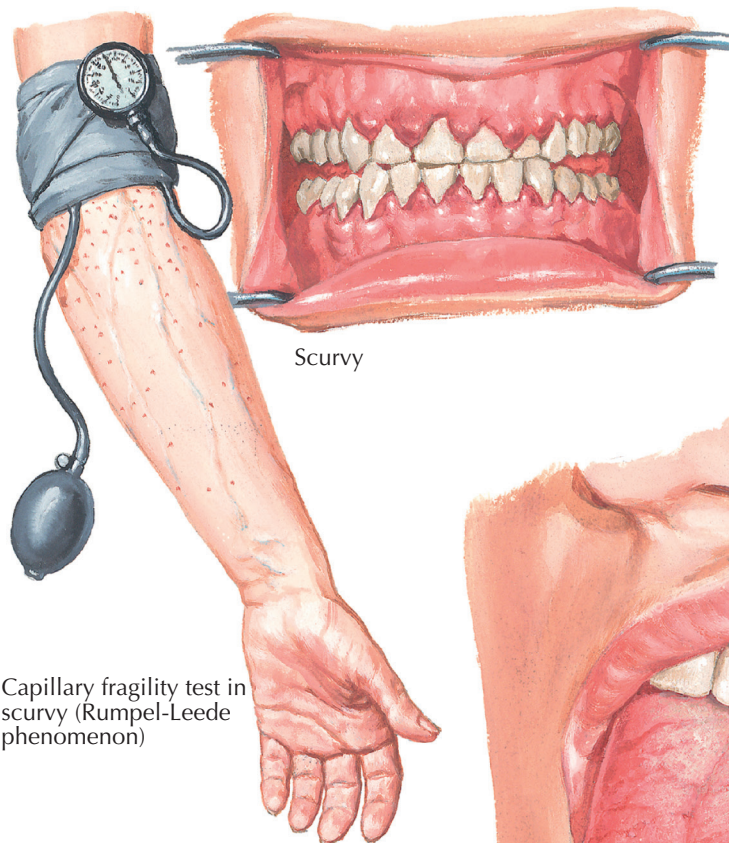
Rose-colored gingivae complicated by frequent bleeding is one of the earliest signs of *scurvy*, or vitamin



Ariboflavinosis



Niacin or nicotinic acid deficiency (pellagra)

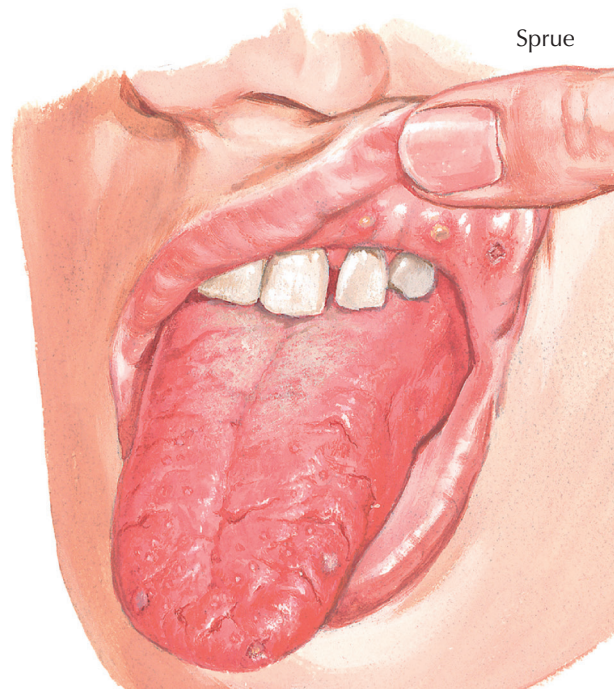


Scurvy

Capillary fragility test in scurvy (Rumpel-Leede phenomenon)



Scurvy: Swollen, congested, bleeding gums



Sprue

C (ascorbic acid) deficiency. In later stages, the gingival papillae become enlarged, bluish red, and spongy; the teeth become loose; salivation increases; and an oral fetor appears. The bleeding tendency of the gingivae is part of a generally increased capillary fragility, which may be ascertained by producing the *Rumpel-Leede phenomenon* (appearance of petechiae in an area following the application of vascular constriction).

Celiac sprue is characterized by small bowel malabsorption due to villous atrophy resulting from an anti-

genic reaction to ingesting wheat gluten or similar grains, which can produce oral symptoms. A burning of the oral mucosa and tongue appears after episodes of diarrhea. Numerous vesicles may form; a scarlet color and aphthous lesions and fissures make a "sprue tongue" closely resemble a pellagra tongue. Iron deficiency anemia results from poor absorption of iron; reduced iron stores, most often due to chronic blood loss and poor dietary intake of iron, can cause pallor of the lips and mucous membranes.

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ORAL MANIFESTATIONS IN HEMATOLOGIC DISEASES

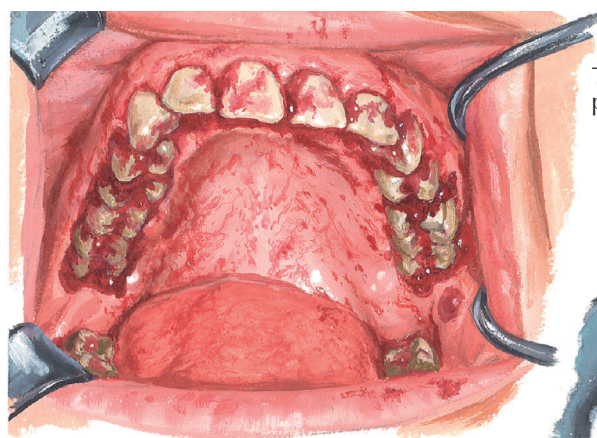
Though oral manifestations in hematologic disorders typically appear after disease progression, bleeding from or texture or color changes of the oral mucosa can be the presenting symptom.

The prominent oral signs of *thrombocytopenic purpura* include widespread capillary oozing from the gingival margin of all the teeth. From adherent clots a fetid odor may emanate. Spontaneous hemorrhages of greater severity may arise, especially in areas of inflammation. Petechial spots also appear as purplish red patches on the lips and other mucosa. Erosion and ulcerations are seen only in debilitated, advanced cases.

In the acute phases of *agranulocytosis*, ulcerative lesions of the mouth and pharynx, accompanied by dysphagia, are frequently seen and may be the initial presentation of the disease. The disease may be acute or chronic (cyclic and recurrent); it may be primary or a sequel of a systemic infection, hormonal dysfunction, or idiosyncratic drug reaction. Because the myeloid cells are arrested in maturation, the mucous membranes are subject to rapid invasion of bacteria. With sudden onset the oral mucosa is involved by necrotic ulcers, which show little or no surrounding erythema. All types of gingivitis and stomatitis with gangrenous areas have been observed in the pharynx, tonsils, and hard palate. Malodorous breath and excessive salivation can be seen in severe presentations.

The frequency of oral lesions in *chronic leukemia* is appreciable and varies considerably in severity. Beginning insidiously, pallor of the mucous membrane may be followed by soft hypertrophy and ulceration of the gingivae, with spontaneous bleeding, and fusospirochetal infection in necrotic papillae, producing a foul odor. A blackish, pseudomembranous exudate may cover the tongue, gingivae, and fauces. Enlargement of the gingiva begins usually in the lower interior region. Teeth may loosen, and pulpal liquefaction or abscessed pulps with odontalgia may appear. In the lymphatic form the lymphoid structures of the floor of the mouth and tongue, together with the submandibular lymph nodes, may become enlarged. In general, the acute leukemias produce symptoms more severe than the chronic variants.

In *polycythemia vera* (erythremia, or Vaquez disease), the skin and oral tissues show a vivid purplish red discoloration. Superficial vessels are distended, and the



Thrombocytopenic purpura



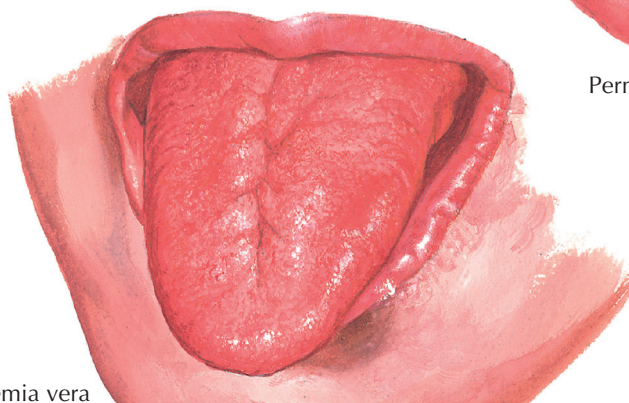
Leukemia (chronic)



Agranulocytosis



Pernicious anemia



Polycythemia vera

gingivae are swollen and bleed frequently. Petechiae are often noted.

In *pernicious anemia*, the oral mucosa accepts a pale or greenish yellow color, except for the tongue, which is bright red. The latter is in a state of chronic inflammation, characterized by irregular, fiery-red patches resembling a burn, near the tip and the lateral margins (*Hunter* or *Moeller glossitis*). A sensation of burning, itching, or stinging is always present, and patients complain of paroxysmal pain or tenderness to food intake

or to cold and hot fluids. These symptoms appear in the early stages of pernicious anemia, sometimes prior to or during periods of hematologic remission. The later stages of the oral manifestations, including the gradual loss of the papillae and progressive atrophy of the tongue, are rarely encountered. Tongue manifestations of the disease must be distinguished from other forms of glossodynia and glossopyrosis, from allergic lesions, from the lingual manifestations in syphilis, and from geographic tongue.

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ORAL MANIFESTATIONS IN VARIOUS SKIN CONDITIONS

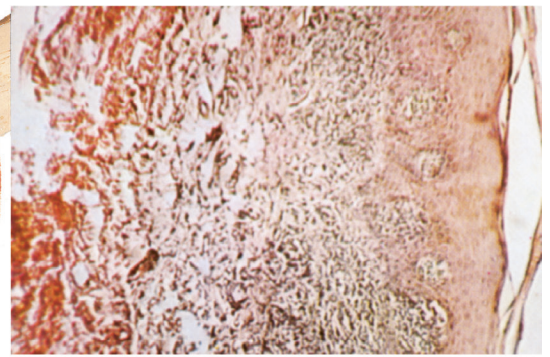
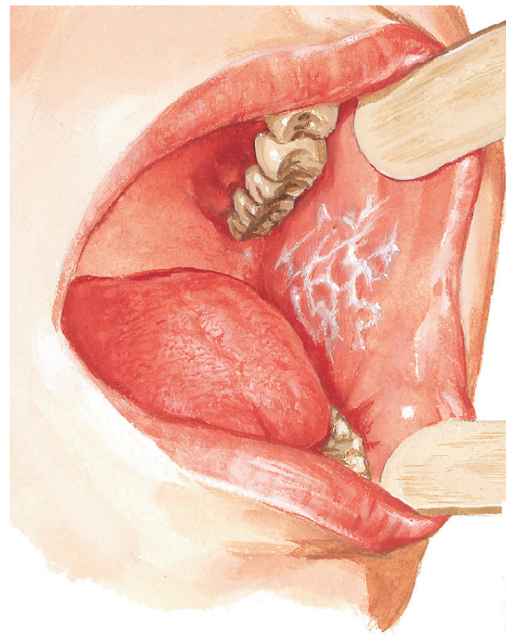
A great number of pathologic conditions of the skin have accompanying oral manifestations that may precede or occur concurrently with or independent of the cutaneous eruption. In general, such lesions do not bear strict comparison with the skin lesions, because of the considerable difference in moisture, temperature, exposure to trauma, lack of a keratin layer, and the presence of secondary infection. In the differential diagnosis the prevalence of purely local lesions of a vesicular or bullous type (e.g., recurrent aphthous ulcers) should be kept in mind.

One of the familiar dermatoses in which the oral mucosa may participate is *lichen planus*, which is a chronic inflammatory disorder with no malignant potential. It has the appearance most commonly of rectangular white plaques associated with erythema and erosions; less often seen are ulcerations and hyperkeratotic plaques. The pathogenesis has not been completely elucidated, but it involves a T cell-mediated immune response causing a cytotoxic reaction by activating CD8 T cells against epithelial basal cells. The diagnosis is confirmed through a review of the patient history, physical examination, and histologic findings. The presence of the purplish, polygonal, or angular skin papule eruptions improves the accuracy of the diagnosis. In a majority of cases, however, the oral lesions precede those of the skin surfaces, and, not infrequently, the disease may remain confined to the mouth. Most often, the cheek mucosa displays the characteristic fine, lacelike pattern of bluish white lines and small, pinhead-size, elevated papules, although the tongue, palate, and gingiva may be similarly affected. The latter locations, as compared with the cheek, usually show coarser plaques and aggregated papules. The lips are least commonly involved. Occasionally, an erosive form may be observed, which is painful and characterized by a caked, whitish material covering a red base in which bleeding is easily induced. The radiating and interlaced grayish white lines are the most significant signs in the diagnosis. These lesions are most often seen in HIV/AIDS and other immunosuppressed conditions.

Differentiation from syphilis, moniliasis, and glossitis migrans is easily made, but differentiation from other local leukokeratoses is sometimes difficult, and biopsy then becomes a helpful adjunct. The histopathologic picture in lichen planus shows moderate keratosis or parakeratosis, a "sawtooth" arrangement of the rete pegs, and a very typical band of lymphocytes chiefly concentrated beneath a vague basal cell zone. This lymphocytic infiltrate is sharply demarcated from the rest of the stroma.

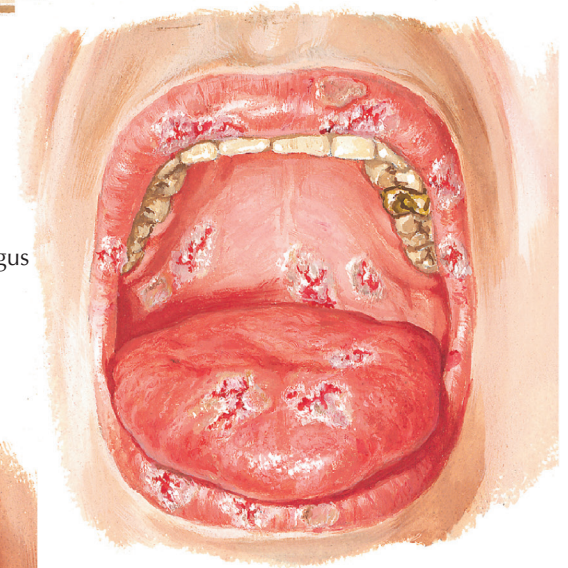
Pemphigus begins in over 50% of cases with manifestations on the oral mucosa, where large, painless vesicles or bullae develop. The thin-walled blebs rupture in a short time, leaving a superficial ulcer rimmed with tattered, grayish shreds of thin membrane. Signs of inflammatory reactions are absent in the early stages but may present themselves later in the form of a slightly red halo. The onset is insidious, chronicity and recurrence being typical even when unaccompanied by skin signs. As the disease progresses, confluent areas become raw and oozing, and salivation, pain, and bleeding increase; mastication and swallowing are impaired.

Erythema multiforme major may affect, along with the skin, the mucous membranes of the mouth, eyes, and anogenital regions. *Erythema multiforme minor* presents similarly but without any mucosal involvement. Both the major and minor forms have the distinctive target skin lesions. The earliest vesicular lesions in the mouth



Left, Buccal lichen planus (lacelike reticular white keratotic striae pattern). Above, Histologic lichen planus (dense subepithelial lymphocytic infiltrate)

Ruptured bullae seen in mucosal pemphigus



Bullous stomatitis seen in erythema multiforme

are sometimes indistinguishable from those of pemphigus. A diffuse bullous stomatitis ensues, with a heavy yellowish pseudomembrane, a marked variation in the size of the lesions, and, often, a bluish red areola around the lesions. The lips are usually swollen, ulcerated, and covered with hemorrhagic crusts. The severity of the disease varies. Recurrence is common and tends to be seasonal. Although the development of erythema multiforme has been linked to many factors, including but not limited to, medications, malignancy, autoimmune disease, and herpes simplex virus infection, the virus is the precipitating agent in over 90% of cases.

Stevens-Johnson syndrome is a rare acute, life-threatening mucocutaneous disease that is nearly always triggered by a drug. Most often the offending agents are allopurinol, anticonvulsants, antimicrobial agents, and nonsteroidal medications. The cutaneous reaction includes extensive keratinocyte cell death causing separation of areas of skin at the dermal-epidermal junction. The oral mucosa and the vermillion border are almost invariably involved with painful hemorrhagic erosions covered with a grayish white membrane. Stomatitis and mucositis lead to impaired oral intake, with consequent malnutrition and dehydration. The degree of body

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ORAL MANIFESTATIONS IN VARIOUS SKIN CONDITIONS

(Continued)

surface area involved in the skin separation process in Stevens-Johnson syndrome is up to 10%. *Toxic epidermal necrosis* is a further progression of the cutaneous process, resulting in involvement of more than 30% of the body surface area. If the involvement is between 10% and 30%, the disease is classified as a combination of Stevens-Johnson syndrome and toxic epidermal necrosis.

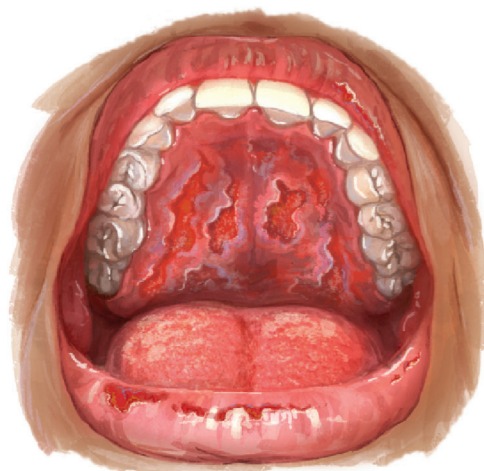
Acquired epidermolysis bullosa is an autoimmune subepithelial blistering disease that primarily affects elderly individuals; it has no predilection for gender or race. The skin eruption is generalized and favors skin folds and flexural areas. The initial presentation is an area of localized erythema or urticarial papules that coalesce into plaques and subsequently turn into dark-red vesicles and bullae in a few weeks. Oral blisters can develop; they are few in number and are less severe and more transient than the cutaneous lesions. *Hereditary epidermolysis bullosa* is a heterogeneous group of genetic bullous disorders characterized by blister formation in response to mechanical trauma. The dystrophic and junctional types are more serious and include organ involvement, skin breakdown, and scarring. Enamel hypoplasia is present in, and limited to, the junctional form, causing pitting of the deciduous and permanent surfaces of the teeth. Dental caries is prominent in both the junctional and dystrophic forms of the disease. None of the serious cutaneous or oral manifestations have been described in the simplex form of the condition.

Langerhans cell histiocytosis (histiocytosis X) is a rare disorder characterized by organ infiltration of Langerhans cells. Papules, vesicles, nodules, and a seborrheic-like pattern on the scalp and diaper area are the primary cutaneous findings of the disease. Dental problems are seen in 30% of patients, and they include a destructive periodontitis resulting from osseous infiltration of the Langerhans cells. Ultimately this can cause destruction of the dentition support system from the maxilla and mandible and loosening of the teeth (*floating teeth*). Periodontal involvement characterized by gingival recession and pocket formation ultimately leads to alveolar bone loss, culminating in loss of dentition.

Congenital erythropoietic porphyria is a rare autosomal recessive disorder that is phenotypically depicted as an abnormality of heme biosynthesis. A pale oral mucosa and teeth that appear a red-maroon color (*erythrodonia*) are the primary dental abnormalities seen. The pattern of discoloration is distinct and aids in the diagnosis. The incisors are nearly completely stained, whereas the canines are colored at the cusp tips and the molars demonstrate varying degrees of discoloration. The coloring of the teeth is thought to be from an affinity of porphyrins for the calcium phosphate-rich teeth.

Congenital syphilis is a result of transplacental infection by *Treponema pallidum*. Cutaneous findings of red macules and papules, a papulosquamous eruption, or a desquamating dermatitis are seen in less than half of the infants infected, but hemorrhagic bullae on the palms and soles are pathognomonic of the infection. Rhinitis, mucous patches on the lips, mouth, tongue, and palate, and condylomata mainly in the anogenital area and angles of the mouth are characteristic.

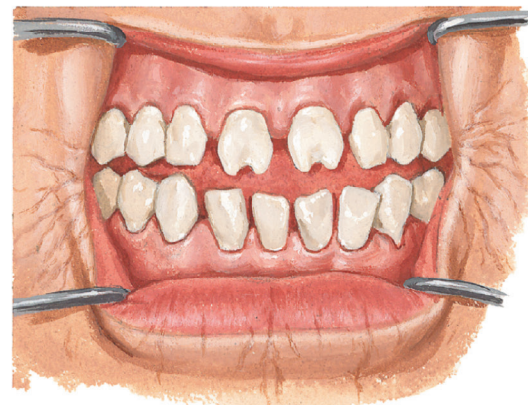
Ectodermal dysplasias constitute a group of hereditary conditions characterized by one or more ectodermal structures, including the skin. The typical areas affected are the hair (hypotrichosis, partial or complete alopecia), nails (dystrophic, hypertrophic, or abnormally



Pemphigus vulgaris. Mucocutaneous changes of Stevens-Johnson syndrome



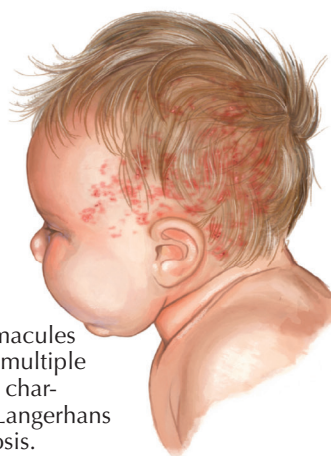
Paraneoplastic pemphigus. Severe mucocutaneous lesions seen with disease progression of Stevens-Johnson syndrome.



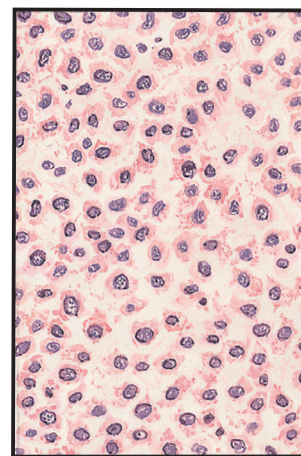
Congenital syphilis: Hutchinson teeth



Facial angiofibromas (adenoma sebaceum)



Papules and macules studded with multiple petechiae are characteristic for Langerhans cell histiocytosis.



Sheets of Langerhans cell histiocytes with abundant pink cytoplasm and folded nuclei with prominent nuclear grooves

keratinized), tooth enamel (defects or absent), and hypoplastic or aplastic sweat glands. Dental defects are characteristic and a core manifestation of the disease, including anodontia, polyodontia, dysplastic teeth, retained primary teeth, deficient enamel development (amelogenesis imperfecta), and underdevelopment of the alveolar ridge.

Tuberous sclerosis (Bourneville disease) has an autosomal dominant inheritance. It results in the formation of hamartomatous lesions in several organ systems, including the skin, brain, kidney, ear, lung, bone, and eye. Characteristic oral lesions include gingival fibromas

and dental enamel pits caused by a reduced amount of enamel present during dentition development. The pits are large defects in the enamel without a change in color or texture of the enamel surrounding the pit, producing a pockmarked appearance.

Nevoid basal cell carcinoma syndrome is an autosomal dominant predisposition for the development of epitheliomas, medulloblastomas, and other developmental abnormalities. The hallmark of the disease, however, is the presence of multiple odontogenic keratocysts. Finding the keratocysts in a young child is diagnostic of the condition.

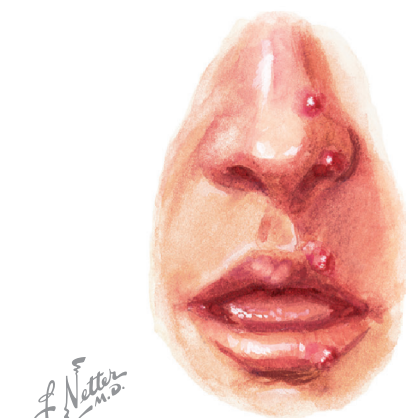
ORAL MANIFESTATIONS OF IMMUNOCOMPROMISED CONDITIONS

Human immunodeficiency virus (HIV) infection, bone marrow transplantation, solid-organ transplants, irradiation, and chemotherapy account for most immunosuppressive conditions. Typically the oral manifestations associated with HIV and other immunosuppressive conditions can be attributed to one of five etiologic categories: fungal, as in oral candidiasis; bacterial, as in gingivitis; viral, as in leukoplakia (see Plate 2-41); neoplastic, as in Kaposi sarcoma; and miscellaneous. It has been reported that up to 50% of patients with HIV develop oral lesions during the course of the illness; however, in the era of highly active retroviral therapy (HAART), the incidence of oral candidiasis, hairy leukoplakia, and Kaposi sarcoma has decreased significantly. The effect of HAART on periodontal disease remains less clear. *Linear gingival erythema*, formally called *HIV-associated gingivitis*, is typically found in the gingiva along the anterior teeth line in immunosuppressed individuals. When seen in HIV-infected patients, there is an increase in polymorphonuclear lymphocytes compared with nonimmunosuppressed patients. Oral candidiasis is often associated with this lesion. Although typically associated with the formation of plaque, improvements in oral hygiene and gingival debridement do not improve this condition. The sublingual plaques are associated with increased amounts of bacteria; therefore, therapy includes professional plaque removal and supplementation with antimicrobial oral rinses. *Necrotizing ulcerative gingivitis (NUG)* is limited to the gingival tissue without loss of periodontal clinical attachment. In contrast, *necrotizing ulcerative periodontal (NUP) disease*, also seen in the immunosuppressed population, involves the periodontal ligament and destruction of the alveolar bone. In these cases, therefore, the disease may include constitutional symptoms of fever, malaise, malodorous breath, and local lymphadenopathy. In patients with HIV, NUG is typically not seen until the CD4 count falls below 500 cells/mm³ whereas NUP is most often seen in those with CD4 counts below 200 cells/mm³. Although HAART therapy should decrease the incidence of these conditions, progression of quiescent disease to symptomatic disease has been reported with the initiation of HAART.

Recurrent labial and intraoral *herpes simplex infection* is more common in HIV-infected than non-HIV-infected individuals. These oral lesions begin with the formation of a vesicle that ulcerates and crusts over in extraoral locations. Herpetic lesions typically affect the keratinized mucosa of the gingiva, beginning as very small (1 to 2-mm) rounded ulcerations that can increase in size and coalesce to form a single larger ulceration. Although the gingiva is most often the site of origin, they can occur less often on the palate and tongue.

Cytomegalovirus infection is less often seen in HIV patients and more often seen in immunosuppressed individuals following bone marrow or organ transplantation. The infection can cause painful oral mucosal ulcerations characterized by a punched-out appearance with nonindurated borders without any surrounding edema. These are typically seen on the lips, gingiva, tongue, buccal mucosa, and pharynx.

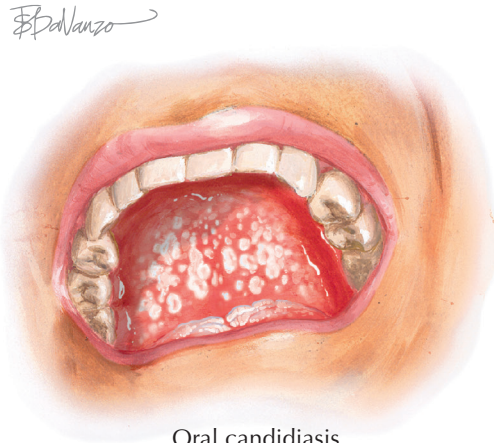
Oral warts (condyloma acuminatum) are caused by the human papillomavirus and appear as either verruca vulgaris with single or multiple pink cauliflower-like



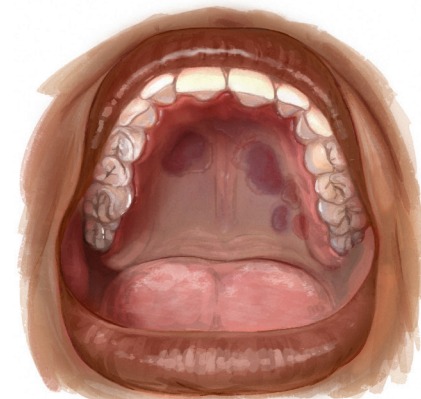
Herpes simplex



Herpes labialis



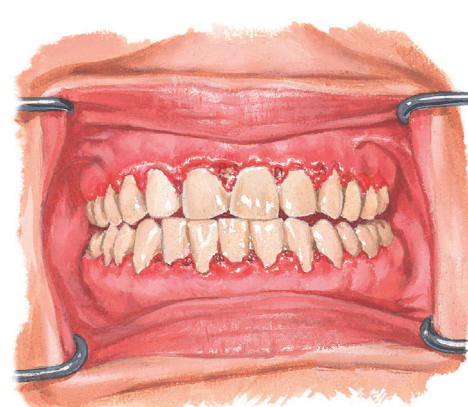
Oral candidiasis



Kaposi sarcoma



Oral wart



Necrotizing ulcerative gingivitis

nodules, papillomas with white spikelike projections, or focal epithelial hyperplasia with flat pink papules. The warts are asymptomatic, variable in size, and primarily seen in the lips, gingiva, and buccal, labial, and palatal mucosa. Oral warts occur in 1.2% of HIV-infected individuals. Malignant transformation may occur in this population.

Oral candidiasis is most often a result of infection by *Candida albicans*; less often by *C. glabrata*, *C. krusei*, or *C. tropicalis*; and even less often by other *Candida* species. It is the most common infection in patients with immunocompromised conditions or who are receiving immunosuppressive therapeutic regimens. Pseudomembranous candidiasis (*thrush*) is characterized by single to multiple white, creamy, curdlike plaques located on any oral mucosal surface. When they

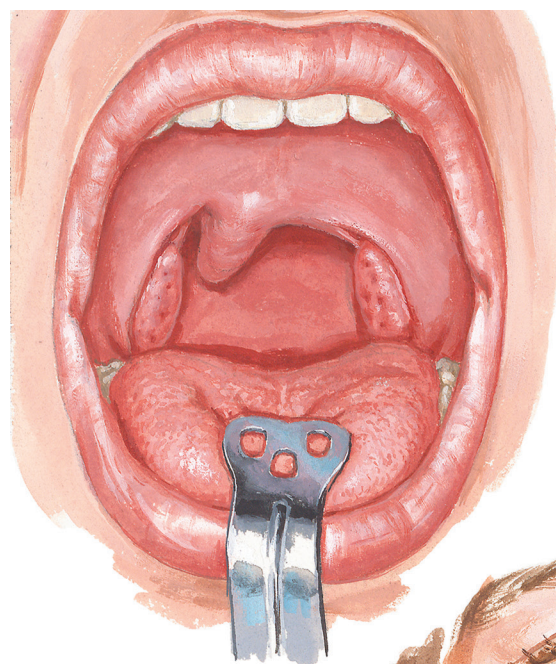
are wiped off, superficial bleeding may be revealed, and in rare instances, invasive ulcerations can develop.

Oral Kaposi sarcoma is the most common neoplastic lesion seen with HIV infection. Its development is correlated with the degree of immunosuppression and the CD4 T-cell count. Human herpesvirus type 8 may be the agent responsible for the development of this vascular mucocutaneous neoplasm. The lesions are typically asymptomatic, reddish purple, macular or papulonodular lesions that do not blanch. The most common location in the oral cavity is the palate, followed by the gingiva and tongue. Infrequently the lesions can extend into the alveolar bone of the jaw, resulting in bone destruction and tooth mobility. The lesions can remain localized and quiet, or they can coalesce and cause pain and bleeding.

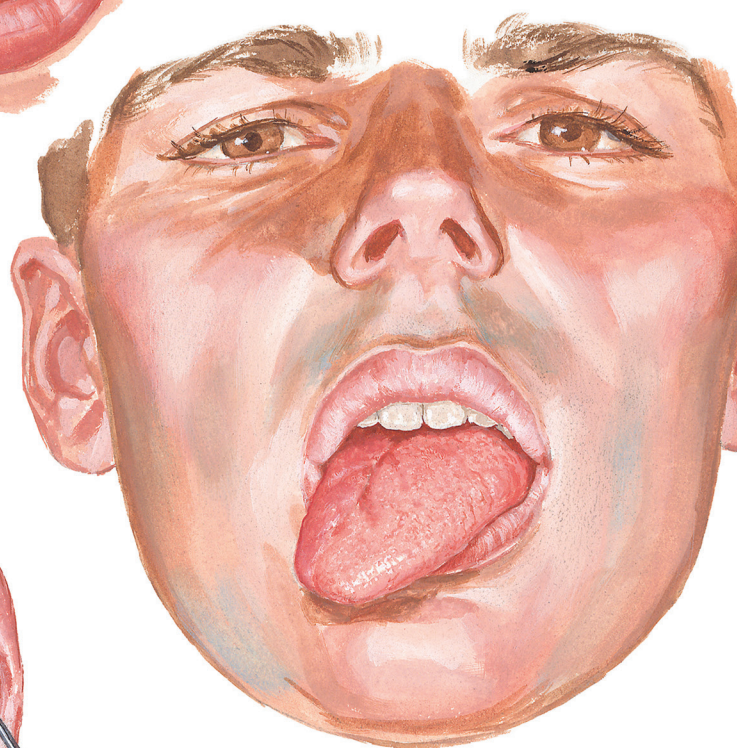
NEUROGENIC DISORDERS OF MOUTH AND PHARYNX

The motor innervation to the pharynx and almost all of the sensory supply is through the pharyngeal plexus, which is formed by branches of cranial nerves IX and X. Disturbances to the neural conduction of both of these cranial nerves will be reviewed together because anatomically and functionally there is considerable overlap in their conductive patterns.

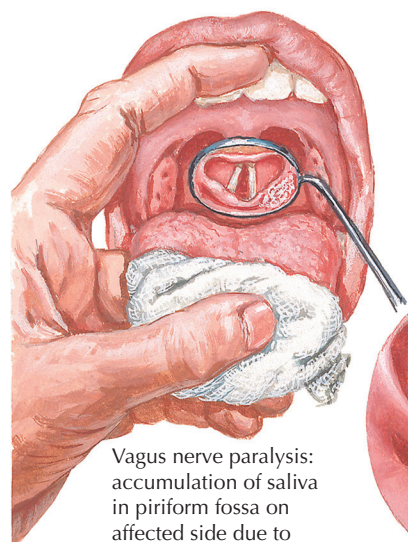
Normally, the *uvula* hangs in midposition, and in case of a *unilateral paralysis*, it deviates to the healthy side. This can be demonstrated when the patient utters "A-AH." In bilateral, peripheral, or nuclear (bulbar) palsy, the uvula does not move at all on attempted phonation or reflex stimulation. On the other hand, in supranuclear (pseudobulbar) palsy, the lower motor neuron reflex is preserved, and the uvula will move on tickling or stimulation with a tongue depressor, but it will not move on willful effort. The loss of pharyngeal reflex can be tested by irritation with a tongue depressor. Deglutition can be examined by having the patient swallow a few mouthfuls of water and observing the upward excursion of the larynx. In paralysis of the soft palate, nasal regurgitation or spasmodic coughing is noted because the fluid is propelled into the nasal cavity, which is incompletely closed during the act of swallowing (*nasal regurgitation*). Nasal and palatal speech, aphonia and dyspnea, and difficulty in swallowing are the essential signs of a vagus paralysis. Because *vagal paralysis* leaves the superior pharyngeal constrictor muscle without innervation, retention of barium and distention of the involved piriform fossa can be demonstrated with a modified barium swallow. Furthermore, it is possible to observe pooling of the saliva in the postcricoid region and in the involved piriform fossa by mirror laryngoscopy or during a fiberoptic endoscopic evaluation of swallowing. The vagal paralysis may be peripheral, as in a postdiphtheritic condition or from a surgical resection; it may be part of a jugular foramen syndrome; or it may have an intracranial origin, as occurs in amyotrophic sclerosis, syringomyelia, or true bulbar palsy. Paralysis may also result from supranuclear involvement (upper motor neuron), as seen usually in multiple vascular lesions producing so-called pseudobulbar paralysis. Normally, the tongue,



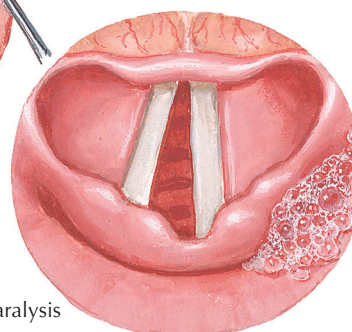
Uvular paralysis: uvula drawn to nonparalyzed side when patient says "A-AH"



Hypoglossal nerve paralysis: tongue deviates toward paralyzed side when protruded



Vagus nerve paralysis: accumulation of saliva in piriform fossa on affected side due to cricopharyngeal muscle paralysis and inability to swallow



which is innervated by the 12th *hypoglossal nerve*, can protrude far out in the midline. In *unilateral paralysis* of this nerve, the tongue deviates to the paralyzed side. In complete bilateral paralysis, the tongue cannot protrude at all and lies flat in the mouth. Unilateral or bilateral paralysis may be associated with atrophy and fibrillation, both indicative of peripheral involvement. Articulation, except for the pronunciation of labials, is impaired. In vagal paralysis the recurrent laryngeal

nerve on the same side is always involved. This produces hoarseness owing to fixation of the vocal fold. In bilateral paralysis, the fold's extrinsic pressure most often assumes the cadaveric position or may become fixed in the midline, producing dyspnea and requiring emergency tracheotomy. Recurrent laryngeal nerve paralysis is most often attributed to surgical trauma, extrinsic compression from enlarged lymph nodes, and local spreading of regional cancers.

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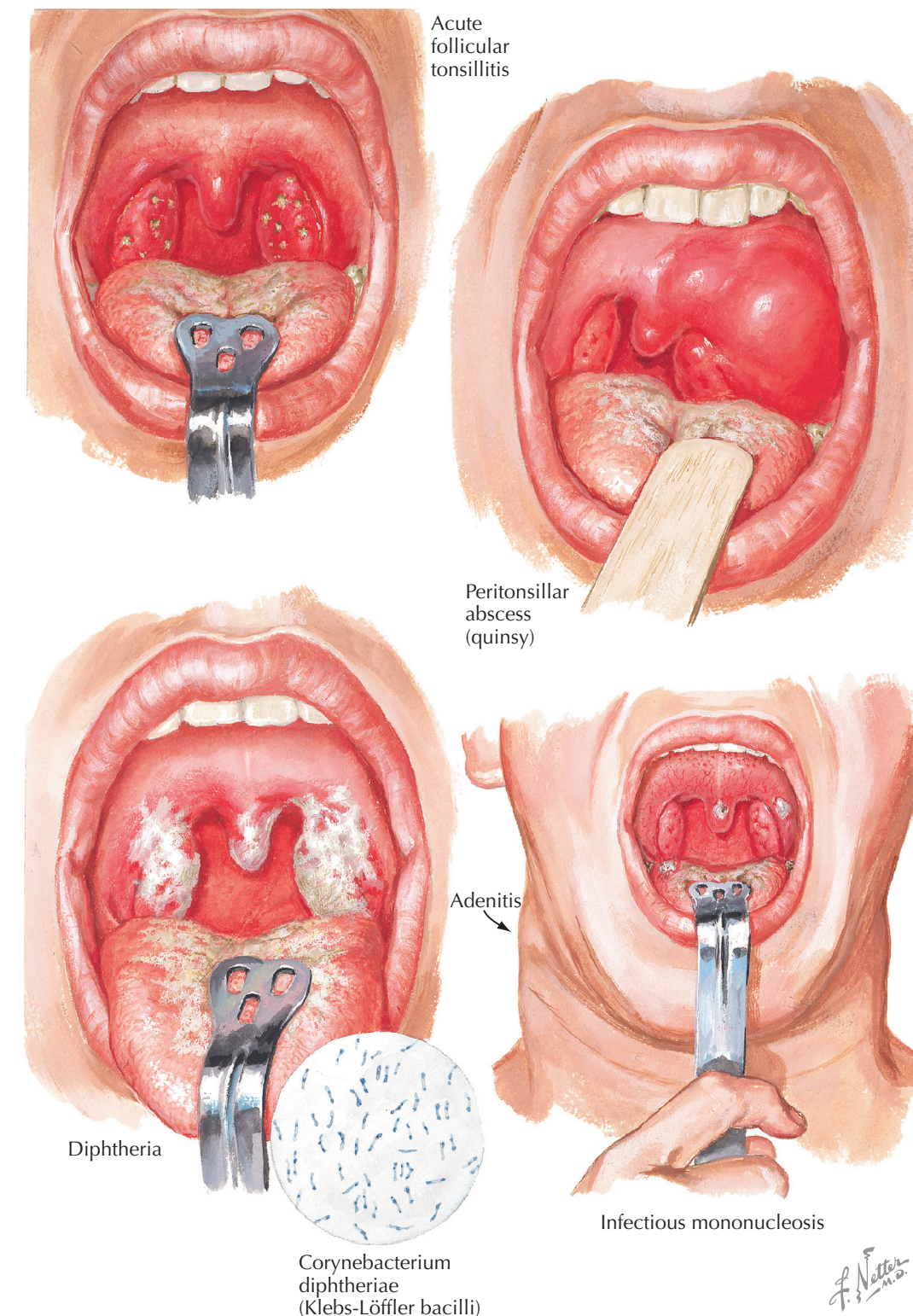
INFECTIONS OF PHARYNX

Acute tonsillopharyngitis caused by group A streptococci (*Streptococcus pyogenes*) is the most frequent organism cultured in infectious pharyngitis. The disease predominantly occurs in children, adolescents, and young adults with hypertrophic tonsils and a history of recurrent infections. Symptoms of headache, chills, throat pain, and fever may develop abruptly. The tonsils are enlarged and inflamed, with a cheesy, rarely coalescing exudate visible in the tonsillar crypts. The infection is usually bilateral; the local lymph nodes are tender and enlarged. Edema of the uvula produces thick, muffled speech and pooling of saliva in the oral cavity. The adenoid tissue and the lingual and pharyngeal tonsils are very frequently involved in the inflammatory process of the infection. A throat culture for the streptococcal organism is the gold standard in the diagnosis; however, a rapid antigen detection test is most often the diagnostic test of choice because of convenience, even though its sensitivity is lower. The infection is self-limiting and resolves in several days; antibiotic therapy will reduce complications and the disease duration, however.

Scarlet fever is a nonsuppurative complication of an acute tonsillitis caused by *Streptococcus pyogenes*, which can produce an erythrogenic toxin responsible for the exanthema and enanthema.

A local complication of acute or chronic tonsillopharyngitis is a suppurative process of the peritonsillar area. A peritonsillar abscess, also known as *quinsy*, may begin to develop during the acute stage of the tonsillitis; however, more often it develops when all symptoms suggest that the patient is recovering from the acute infection. Soreness on swallowing, trismus, marked edema of the uvula and displacement of the uvula to the side opposite to the abscess, ipsilateral earache, and increasing tenderness of the lymph nodes are the early characteristic signs of abscess development, followed by a visible bulge of the anterior pillar of the fauces and soft palate. Occasionally, the swelling may occur in the posterior pillar and displace the tonsil forward. Palpation with the finger and the feeling of fluctuation in the swelling establishes the diagnosis. Spontaneous rupture or surgical drainage brings rapid relief, and antibacterial therapy treats the associated bacterial infection.

Diphtheria, caused by *Corynebacterium diphtheriae* (Klebs-Löffler bacillus), is characterized by membranous inflammation of the pharyngeal mucosa (though many other mucosal surfaces may be a primary site of the infection). The membrane, a raised, yellowish white patch, which may later become brownish and putrid, leaves a raw, bleeding surface if detached. The process is not limited to the tonsillar crypts, as in follicular tonsillitis, but may involve the tonsillar pillars, soft palate, nose, and larynx. The diagnosis can always be made by a smear from the exudate, in which the *Corynebacterium diphtheriae* can be identified morphologically or, more reliably, by culture. Antitoxin therapy is the treatment of choice; it is supported by antibiotics if necessary. Although cardiopulmonary complications are rare, they are life threatening; therefore, primary prevention through immunization is preferred over secondary disease treatment. Since the diphtheria-pertussis-tetanus vaccine was introduced for young children, the number of cases in the United States had been reduced significantly; recently, however, there has been an increase in cases because of adults not receiving a booster to the vaccine and parents opting out of the vaccination program.



With the anginal type of glandular fever, *infectious mononucleosis*, small discrete patches surrounded by an area of erythema are dispersed throughout the throat. They disappear as the infection subsides but may last from 2 to 3 weeks and may recur. Although the adenopathy is generalized, the cervical glands are most often predominantly involved.

Epiglottitis is an acute and often life-threatening infection of the epiglottis, aryepiglottic folds, and adjacent supraglottic structures. *Haemophilus influenzae* type B is the primary infectious agent involved in this process; it invades the pharynx directly or by hemato-

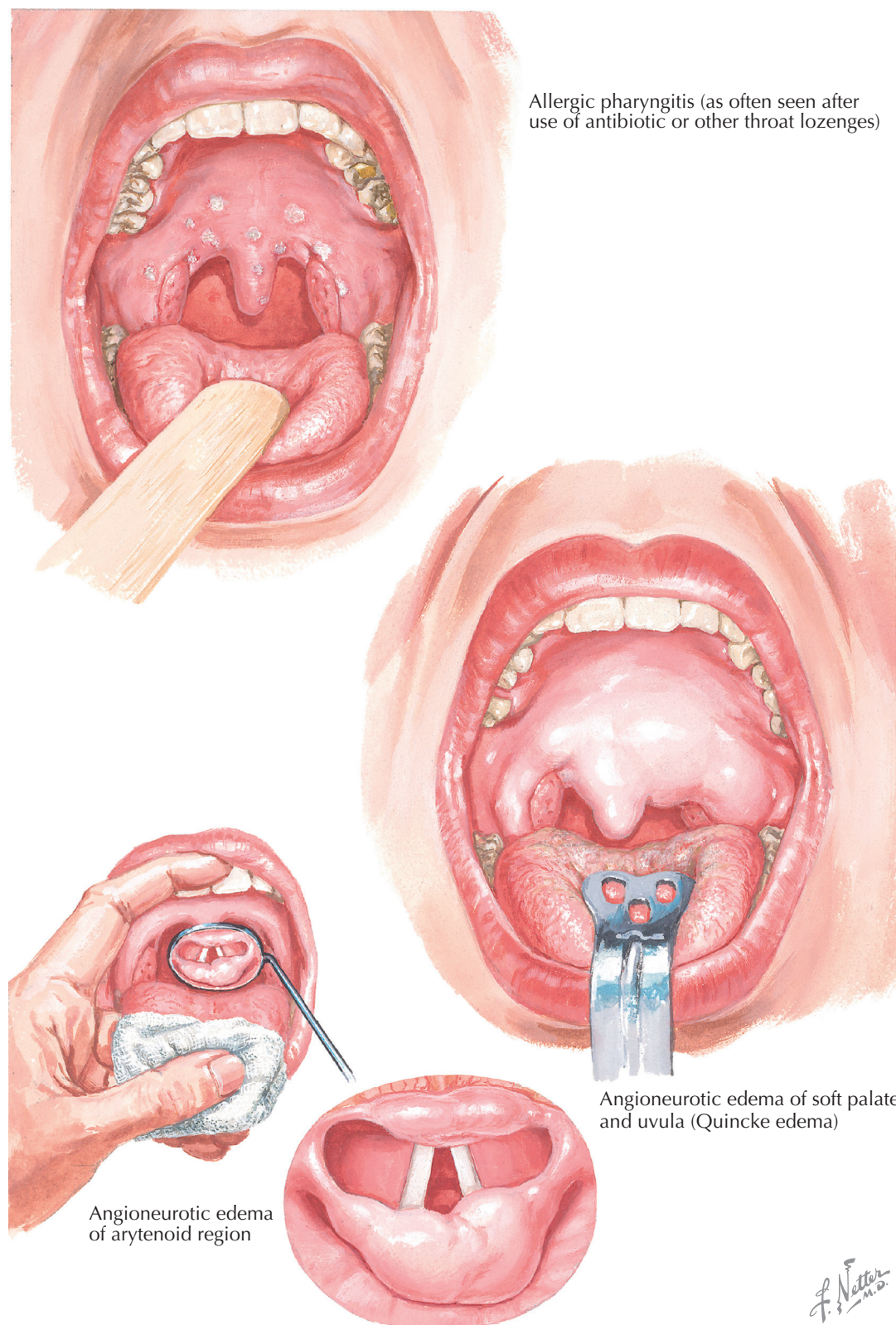
logic spread. The infection most often produces subglottic swelling, which presents as stridor and difficulty breathing. Direct or indirect visualization of the edematous epiglottis is pathognomonic, but the examination may trigger laryngospasm and rapid decompensation. Therefore, lateral neck films may be used to show an enlarged epiglottis protruding from the anterior wall of the hypopharynx (*thumb sign*). Airway management is the primary step in treatment, followed by supportive care. Since the initiation of a vaccination protocol, the number of patients presenting with this infection has decreased significantly.

ALLERGIC CONDITIONS OF PHARYNX

Manifestations of an allergic background may present themselves in the pharynx as independent disorders or may occur in association with allergic symptoms in the skin and elsewhere.

Angioedema is classified as acquired and hereditary. It is a rapid development of edema in the subcutaneous tissue due to extravasation of fluid into the interstitial tissue from a disruption in the vascular integrity. It may occur as a sole presentation, in conjunction with the development of urticarial lesions, or as a medical emergency as an anaphylactic reaction. The pathogenesis of the edema results from inflammatory mediators exerting influence on the capillaries and venules, which causes dilation and increased permeability of the vasculature permitting leakage of fluid into the surrounding tissues. An acute presentation is most often triggered by an allergic reaction to food, drugs, latex, or insect bites. The allergic edema involves not only the exposed mucous membranes but the deeper connective tissues. The involved surfaces are suddenly distended by an edematous fluid of a purely serous variety without an inflammatory reaction. Such swellings can occur in the palate, uvula, or aryepiglottic folds and in the arytenoids. The edema is characteristically in the supraglottis, but isolated involvement of the epiglottis, aryepiglottic folds, and larynx may also produce sudden threatening symptoms of asphyxia. The patient usually complains of an abrupt difficulty in deglutition or respiration associated with a sensation of a swelling or lump in the throat.

In *uvular angioedema*, or *Quincke disease*, the uvula, soft palate, and tonsillar pillars become distended with a pale edema, which protrudes into the pharynx and touches the tongue. Swallowing is impaired, and air hunger may supervene. If the supraglottic structures are involved, a sense of suffocation may be so oppressive that the patient has the feeling of impending death. Epinephrine can be lifesaving when the angioedema may progress to airway obstruction and impending suffocation. The general treatment is similar to that of other allergic conditions, namely, avoidance of the precipitating agent if possible and specific hyposensitization. Antihistamines and corticosteroids are typically effective in relieving the edema. In severe and urgent



Allergic pharyngitis (as often seen after use of antibiotic or other throat lozenges)

Angioneurotic edema of arytenoid region

Angioneurotic edema of soft palate and uvula (Quincke edema)

cases, an emergency tracheotomy may be a lifesaving procedure. Peripheral eosinophilia is an inconsistent finding in the evaluation of atopic disease.

Allergic pharyngitis may be a result of therapy with antibiotics and throat lozenges. Isolated superficial ulcerations, varying by a few millimeters in diameter and surrounded by a small area of erythema, can be seen distributed throughout the soft palate, tonsillar pillars, buccal mucosa, undersurface of the tongue, and lips. These, as a rule, have a whitish membranous covering.

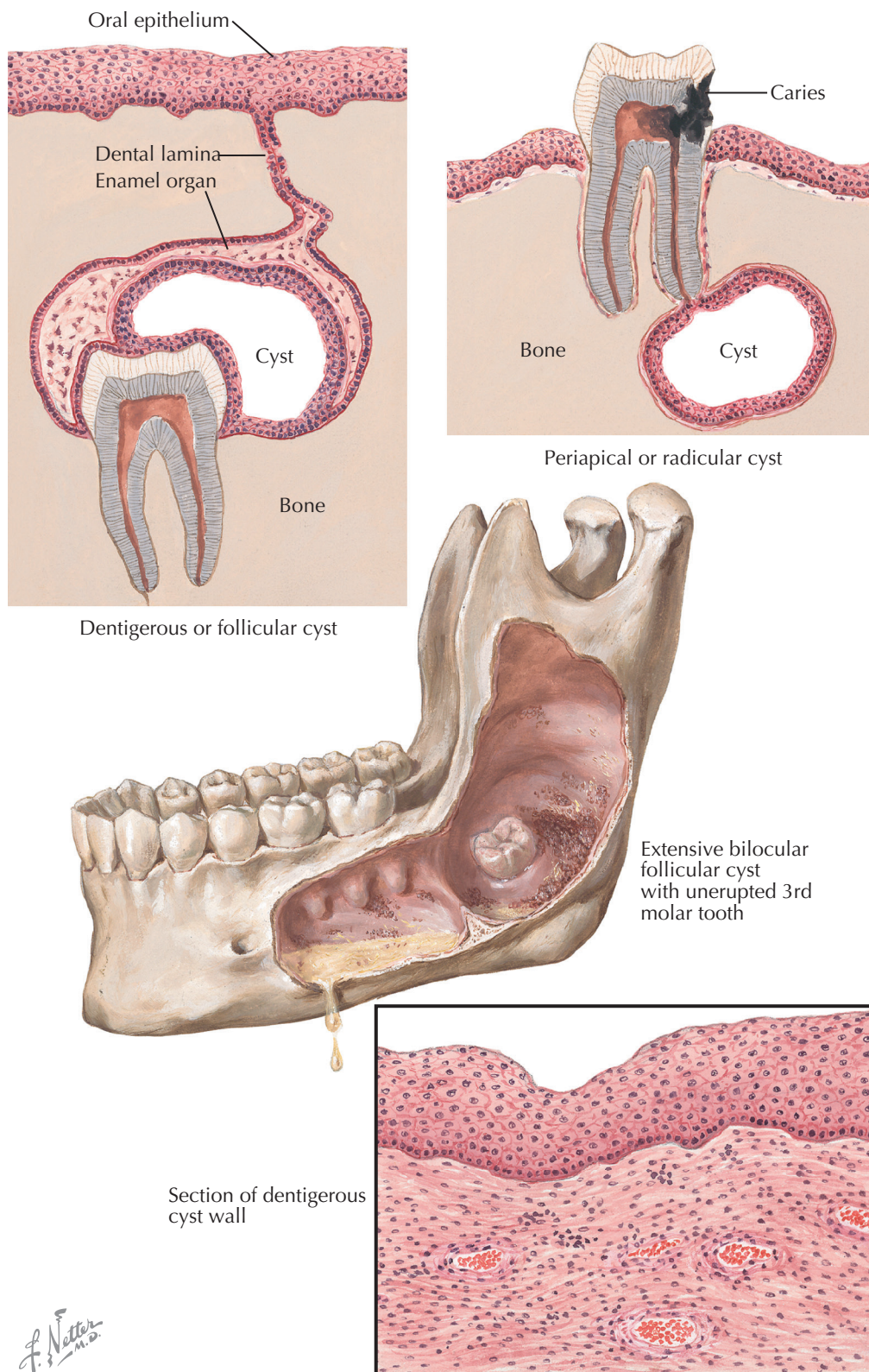
They may result from an antigen present in the lozenge, such as an antibiotic or menthol, which is a common ingredient in lozenges. More often, the ulcerations result from taking broad-spectrum antibiotics; lesions may be produced by an allergy to an antibiotic or by an opportunistic fungal infection incident to the effect of the antibiotic on the normal oral flora. The use of antihistamines and steroids will usually give prompt relief, and avoidance of the offending agent will prevent recurrence.

CYSTS OF JAW AND ORAL CAVITY

Nonepithelialized cysts of the mandible or maxilla may result from trauma with intermedullary hemorrhage, or they may be manifestations of monostotic and polyostotic fibrous dysplasia (disseminated or localized osteitis fibrosa) and generalized osteitis fibrosa, also called cystic osteodystrophy (von Recklinghausen disease). Because the latter conditions are systemic disorders of the bones or endocrine system (primary or secondary hyperparathyroidism), they will not be discussed in this volume. The lesions are more often solid than fluid in content and are recognized as cysts chiefly by their radiographic appearance.

The epithelialized cysts of the jaws are etiologically divided into radicular, follicular, and facial cleft cysts. The *periapical* or *radicular cyst* has an inflammatory basis and evolves from a granuloma at the root apex of a tooth devitalized by caries or trauma. Bacteria and toxins of the infected pulp canal stimulate proliferation of epithelial remnants left in the periodontal membrane from Hertwig sheath, after it has been ruptured and fragmented by the developing tooth. Eventually, this epithelium lines the necrotic center of the granuloma and thickens, tending to isolate the inflammatory process. A fibrous capsule develops outside the epithelial sac, and the lumen increases by transudation of fluid. Round cell infiltration of the cyst membrane, including the adjacent connective tissue and cellular debris, pus, macrophages, and cholesterol crystals are usually found histologically. Even if the tooth with the granuloma is removed, the cyst remains and may even expand more rapidly as a sterile lesion.

The *dentigerous* or *follicular cyst* arises from the enamel epithelium of the dental follicle forming around the crown of an unerupted tooth. It is a benign, noninflammatory cyst thought to be developmental in origin. Infection is present only when contiguous teeth are coincidentally abscessed. The pathogenesis of follicular cysts begins with retrograde changes and edema in the enamel organ, which, by expansion, assumes various shapes above the developing crown. A *simple follicular cyst* forms before enamel is excreted, arresting tooth maturation or growing entirely separate from the tooth. A *dentigerous cyst* arises at a later phase, after amelogenesis, and gradually envelops the crown, thus interfering with eruption. The tooth may be forced by the cyst fluid to a site remote from its normal position in the jaw. A follicular cyst is usually unilocular, but multilocular forms occur. The most frequent location is the mandibular third molar region. Until the cyst attains a large size and expands the cortical plate of bone, the cyst may remain unrecognized. The buccal, palatal, or alveolar bone may then bulge outward, or the maxillary sinus or nasal cavity may be invaded. The wall of the cyst becomes parchment-thin and yields a crackling sound on palpation. Due to the pressure of the cyst and the crowding of roots, the adjoining teeth are tilted when viewed on radiographic imaging and unerupted teeth are displaced in total. Teeth are not devitalized and



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resorption of roots is not encountered. A smooth, encapsulating layer of cortical bone, a unilocular shape, and the absence of root erosion distinguish a cyst from an invasive neoplasm, ameloblastoma, benign giant cell tumor, and osteitis fibrosa localisata or generalisata. However, a cyst secondarily infected from an adjacent tooth shows an obliterated capsule and appears infiltrative. Also, a few cysts may be multilocular and cannot be completely distinguished from ameloblastoma without biopsy examination. A layer of compact bone

borders the cyst sac, which is composed of fibrous connective tissue lined with epithelium. The latter is stratified squamous, ranging from thin to a considerable thickness; in some cysts, it may be simple columnar. The fluid content is clear and straw colored, with an iridescent sheen imparted by cholesterol crystals, or thick and cheesy from epithelial and hemorrhagic debris.

Facial cleft cysts, also called *fissural cysts*, form at the junction of the embryonic segments that fuse to make

CYSTS OF JAW AND ORAL CAVITY (Continued)

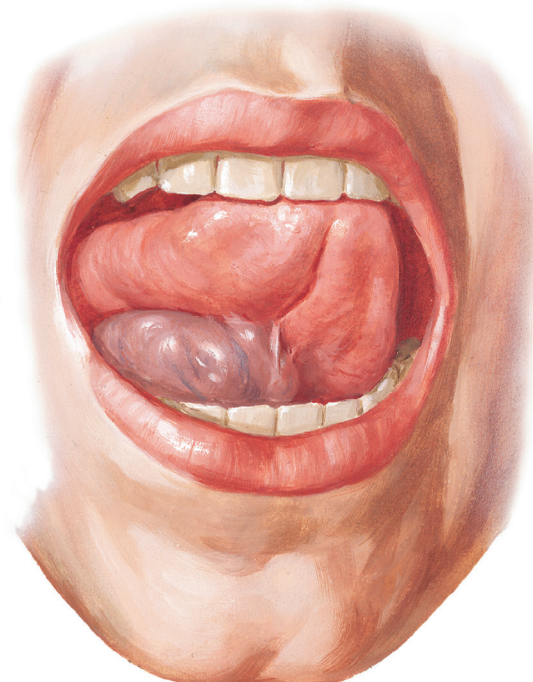
up the jaws. They may be found at the median fissure of the palate, maxillary bones or mandible (midline or median cyst), or nasoalveolar junction. The *nasopalatine cyst*, because it is formed in the incisive canal or the incisive foramen from remnants of the fetal nasopalatine communication, may be grouped with the facial cleft cyst. Irritation or mucous secretions likely play an etiologic role in the more superficial type. Ordinarily, a nasopalatine cyst presents no clinical swelling, unless it is very large, and is detected only on radiographic examination. A radiolucent area appears in the midline between the apices of the central incisor teeth and is often misinterpreted as a radicular cyst. The size varies from slight enlargement of the incisive fossa to one of a few centimeters, involving a higher part of the incisive canal. If retention of serous or mucoid secretion produces swelling in the region of the interincisive papilla, discharge from the two tiny orifices on the side of the papilla may be expressed. Secondary infection may occasionally ensue, producing a fluctuant swelling of the palatal mucosa, resembling a dentoalveolar abscess. Mucopurulent discharge then appears at the incisive outlets on pressure. In edentulous mouths, resorption of the alveolar ridge may expose a nasopalatine cyst that escaped previous detection.

Cysts of the oral mucous membranes are retention cysts of the mucous glands or their ducts or, occasionally, the sublingual salivary gland. The *mucocoele* may appear on the inner surface of the lips or cheeks, especially at a level parallel to the occlusal plane, where chewing injuries cause obstruction of the mucous ducts. A round, translucent, sometimes bluish swelling may range from a very minute size to a centimeter. In the tongue, the glands of Blandin and Nuhn may form more deeply seated mucocoeles, which reach a considerable size, presenting a swelling on the anterior ventral surface.

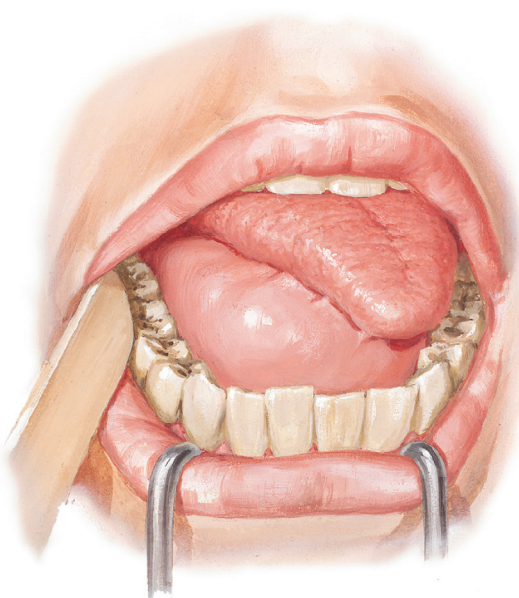
The *ranula* is named for its resemblance to a frog's belly; the term is a rather loose one applied to cystic swellings of the floor of the mouth. A common error is to attribute a ranula to obstruction of the submandibular (Wharton) duct, which in the presence of a typical ranula is found patent. The most frequent cause is the occlusion of an excretory duct of the sublingual gland. In a few cases, a ranula may arise from the incisive glands in the midline or from the ciliated cysts that carry epithelium (Bochdalek "glands"), which are derived from the primitive thyroglossal duct. A typical ranula begins in the lateral anterior floor of the mouth immediately beneath the mucous membrane. It usually grows slowly, but rapidly developing cystic swellings (acute ranulas) are also known. The color is bluish gray, with numerous small vessels well outlined. Palpation gives a decided impression of fluid confined by an elastic membrane; the wall may rupture spontaneously but soon refills. As it reaches large proportions it crosses the midline and shows a division marked by the



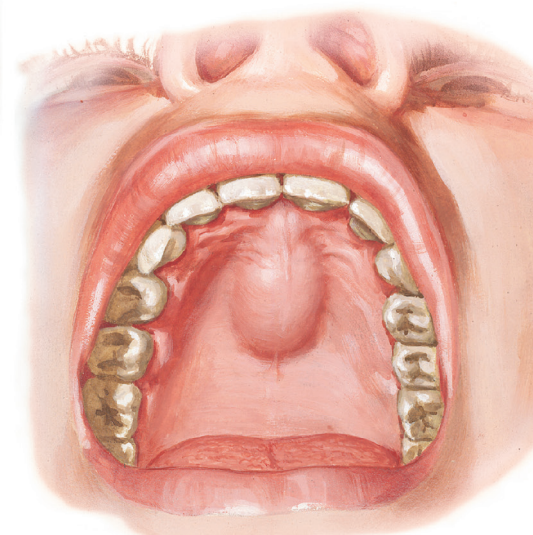
Mucocoele of lip



Sublingual ranula



Sublingual dermoid cyst

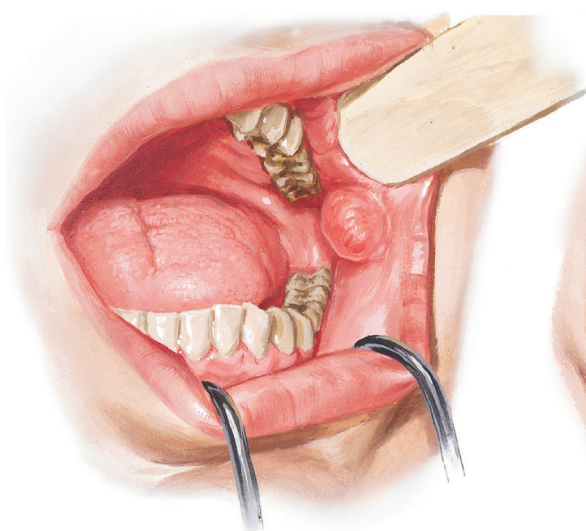


Nasopalatine cyst (secondarily infected)

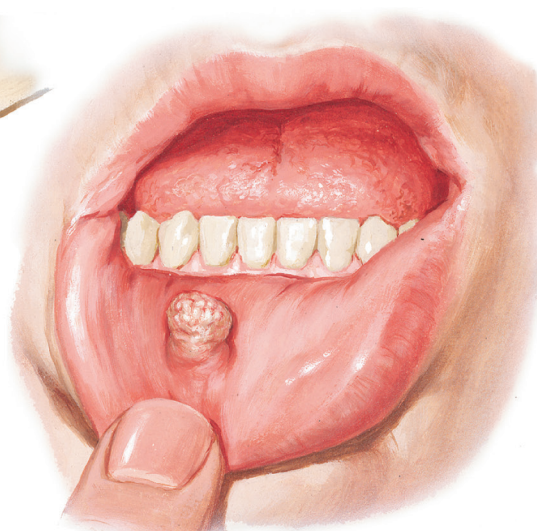
frenulum, also displacing the tongue and impeding speech. A ranula will sometimes bulge downward toward the chin because a portion of the sublingual gland perforates the mylohyoid muscle.

Dermoid cysts, owing their origin to inclusion of ectodermal structures by the mesoderm during the embryonic development of the head, usually become visible only in the second or third decade of life. They are located in the midline beneath the chin or between the geniohyoid muscles deep in the floor of the mouth, or

in a lateral position beneath the angle of the jaw. The cyst consists of a fibrous capsule lined with a stratified, squamous epithelial membrane, with a cheesy or semi-solid mass containing sebaceous material and hair filling the lumen. Theoretically, teeth and other appendages may be present. The dermoid may reach large proportions and protrude in the neck or beneath the tongue as a soft or semifirm doughy lump that pits on pressure and is not fluctuant. The color tends to be waxy or yellowish when the mucosa is thin enough to reveal it.



Fibroma



Hard papilloma

BENIGN TUMORS OF ORAL CAVITY

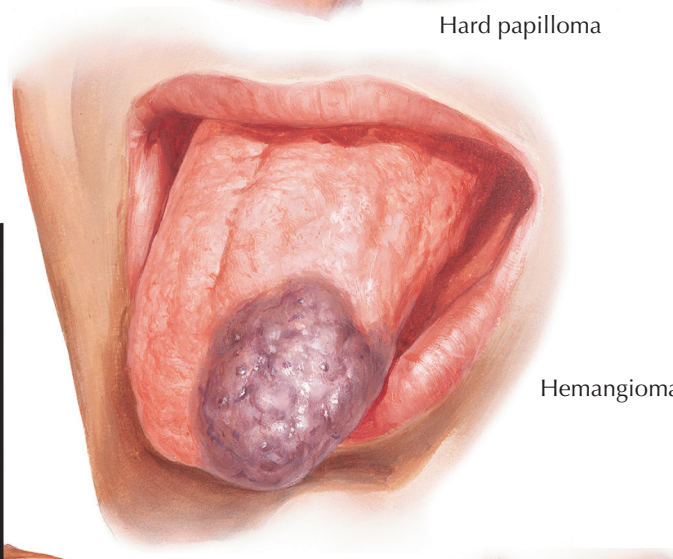
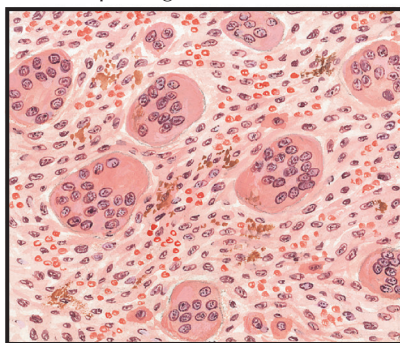
Tumors of the oral cavity are very diversified. Only a select few can be discussed here. A *fibroma* may be found on the gingiva, lips, palate, and buccal mucosa. It is hard or soft and pale or reddish, depending on the density of collagen and the abundance of vascular elements. The gingival fibroma (fibrous epulis) is usually derived from the periosteum. It is sessile or pedunculated, well defined, and slow growing.

The *papilloma* is soft and pedunculated or, when arising from an area of leukoplakia, hard with a warty, keratinized epithelium. The epithelial projections may grow beyond the basal layer and may occasionally curl inward into the stroma and become fixed at their bases, suggesting that they are potentially malignant. They are found in the same areas as the fibromas and also on the tongue.

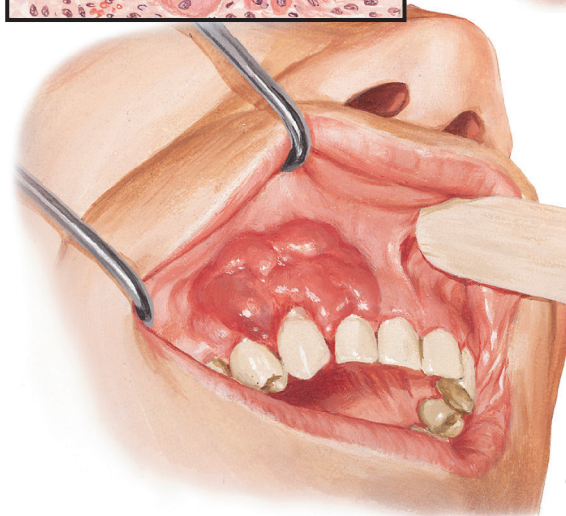
The *hemangioma*, either cavernous or capillary in structure, is primarily seen on the tongue but may arise in any part of the mouth from blood vessel endothelium. It may be congenital or familial, or it may develop at a later period in life. Multiple hemangiomas can occur anywhere in the mucous membrane of the intestinal tract, but the lip, tongue, gum, and rectum are sites of predilection. The color is light red to dark purple, with a tendency to blanch on pressure. Some large hemangiomas appear more globular than flat and are lobulated on their free mucosal surfaces, with a tendency toward displacement of bone by osteolysis. Extension occurs through endothelial proliferation along the nourishing blood vessels, usually more widespread than is apparent on clinical inspection. Significant blood loss has been reported from incidental minor procedures such as tooth extractions.

The *benign giant cell tumor*, or *epulis*, is a not uncommon gingival or, more rarely, an intraosseous growth, which originates from the periodontal membrane or periosteum and has a tendency to recur unless this tissue is widely excised. The superficial form is apparently an exaggerated granulation process, with numerous giant cells eroding the bone trabeculae; older lesions contain more adult fibroblasts and fewer hemorrhages. Extravasation of erythrocytes releasing hemoglobin, which is transformed to hemosiderin, explains

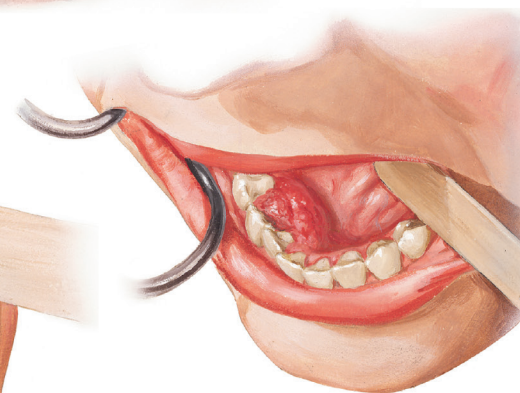
Epulis (giant cell tumor)



Hemangioma



Epulis (giant cell tumor)



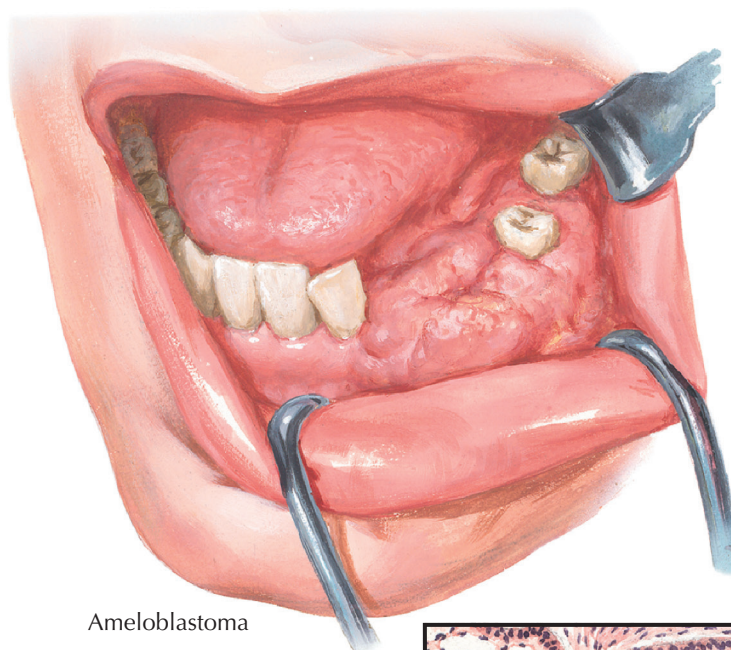
Pregnancy tumor

the occasional brown color. The central giant cell tumor may show features of resorptive inflammation but behaves like a neoplasm and may be identical to the giant cell tumor of the long bones, though it has little relation to giant cell sarcoma. The tumor can, however, infiltrate bone and displace teeth. It is nonencapsulated but does not metastasize. Essentially, it is composed of spindle cells with a varying amount of collagen fibers, hemorrhagic debris, and multinucleated cells. Occa-

sionally, a giant cell tumor on the gum or in the bone is a manifestation of hyperparathyroidism.

The so-called *pregnancy "tumor"* is a hyperplasia, developing in the course of a chronic gingivitis, which is not infrequently observed in pregnant women but sometimes also with other hormonal alterations (e.g., puberty). Bleeding, particularly of the interproximal papillae, with light raspberry to dusky red coloration, is an early sign, followed by a hypertrophic swelling of the

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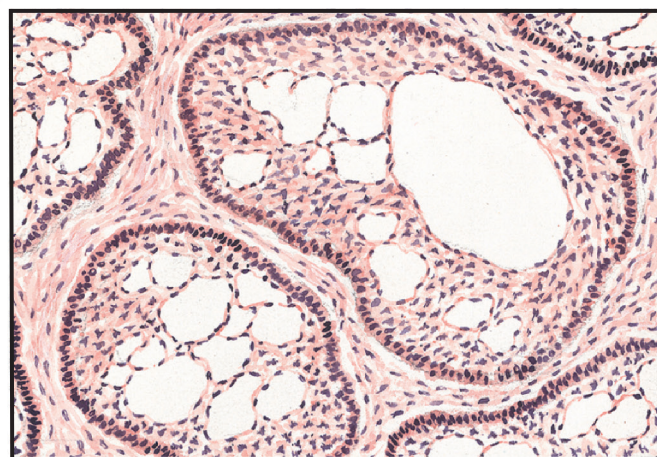
Ameloblastoma

BENIGN TUMORS OF ORAL CAVITY (Continued)

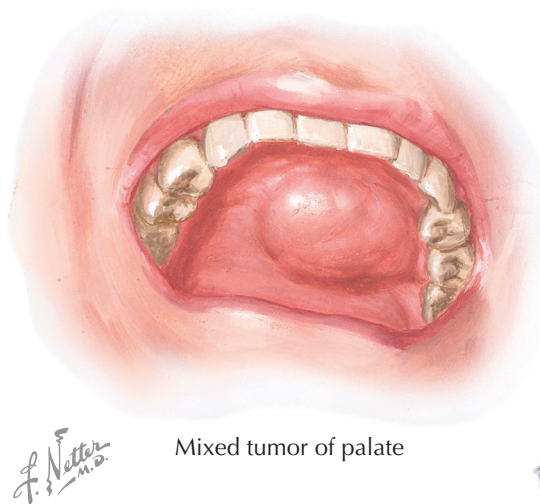
papillary gingiva, ranging from a slight bloating to a tumor of 1 to 2 cm. It may envelop more than one tooth. The growth regresses with proper oral hygiene and adjusted toothbrush technique, though surgery may be required because of constant bleeding. Generally, tumors that are not too large disappear after delivery.

The *ameloblastoma*, sometimes termed adamantinoma or adamantoblastoma, is an epithelial neoplasm occurring chiefly in the mandible (region of the third molar, ramus, or premolar, in that order of frequency); it belongs to the group of odontogenic tumors (as do the myxoma and cementoma) (not illustrated). According to generally accepted belief, the ameloblastoma originates from remnants of the enamel or dental lamina, but from less differentiated cells (preameloblasts) than those producing a follicular cyst. The tumor is mostly polycystic, sometimes monocystic, and occasionally solid. It is this solid form that on rare occasions has been found to metastasize. The growth of this otherwise benign tumor is very slow. Microcystic infiltration, roentgenologically revealed by tiny locules or notching, enlarges the jaw; the only sign is often a tiny bony capsule distending the surrounding tissue. Eventually, expansion into the orbit, antrum, and even cranium may take place. The most common variety, microscopically recognizable, is the ameloblastic type, characterized by follicles resembling enamel, with its outer layer of cylindrical cells and stellate reticulum in the center. Occasionally, solid strands of undifferentiated cells or sheaths of stellate cells or an accumulation of squamous and prickly cells may be found. A microscopic descriptive grading of ameloblastoma is necessary for proper management of each case and for the choice between local or radical removal. The recurrence rate of ameloblastoma is extremely high, but true malignancy is extremely low.

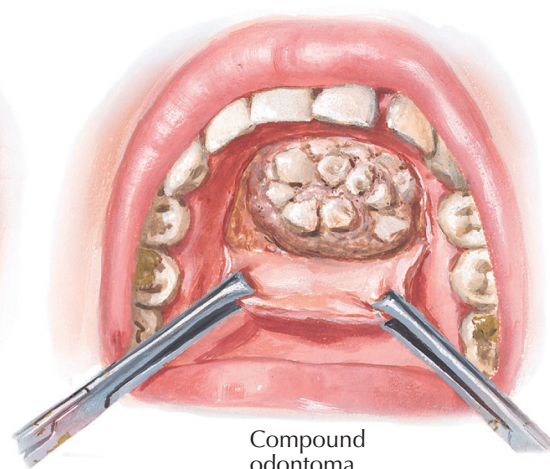
Made up of mixed ectodermal and mesodermal tissue, the *odontoma*, also odontogenic in origin, may be a hard or soft tumor, depending upon the presence or absence of calcified accretions. The hard odontoma is composed of abnormally arranged enamel, dentin, and cementum, in a soft fibrous matrix that is gradually



Ameloblastoma



Mixed tumor of palate



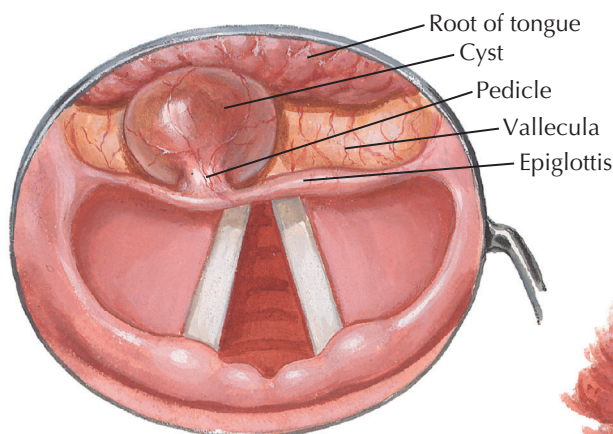
Compound odontoma

replaced by the calcified elements, leaving a capsule. *Complex odontomas* contain a bizarre conglomeration of hard structures without finite shape; *compound odontomas* include both rudimentary and apparently normal supernumerary teeth, at times numbering several dozen. These structures may erupt and imitate the normal dentition.

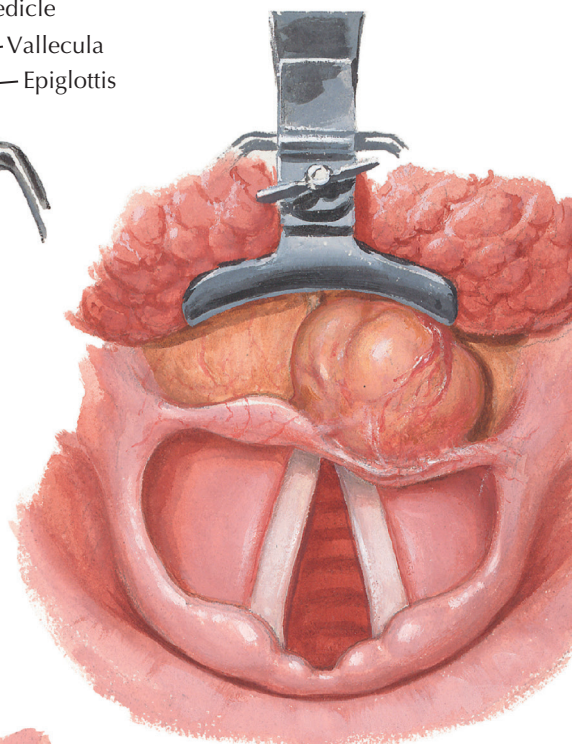
Myxoma of the jaw (not illustrated), derived from embryonal tissue of the dental papilla, is also a benign

odontogenic tumor, as is the cementoma, a special form of fibroma, which appears usually at the apices of the lower anterior teeth. Multiple cementomas appear only in women, suggesting an estrogenic influence.

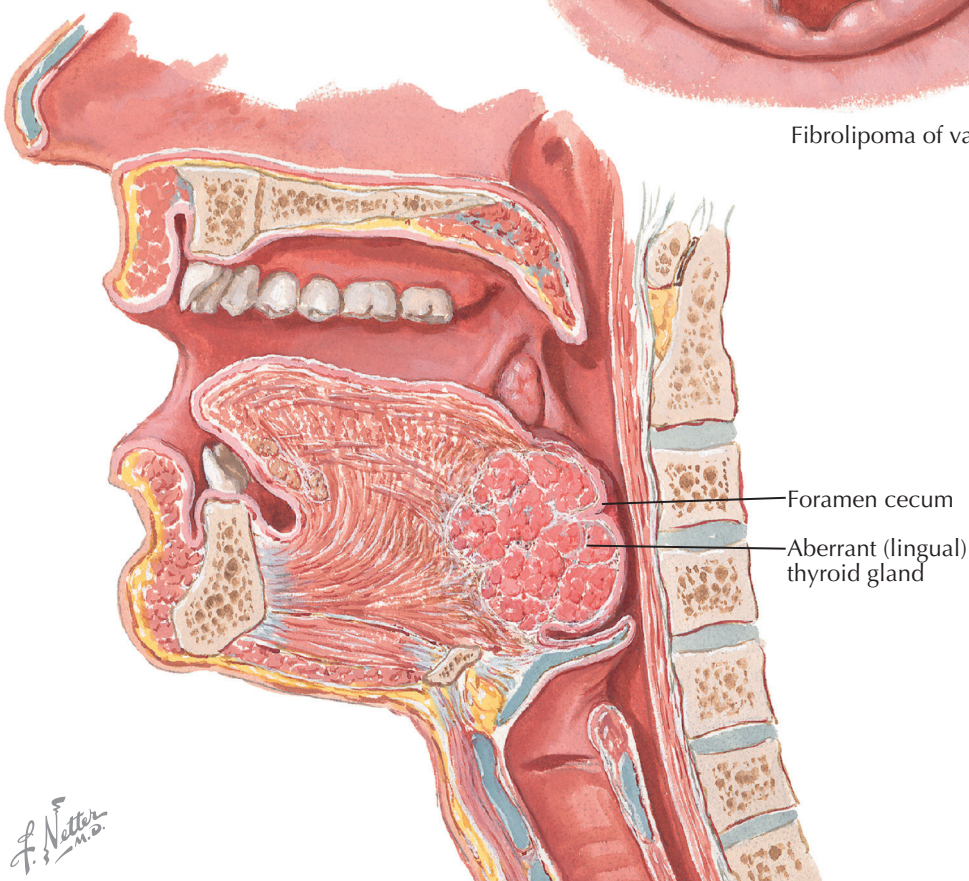
Osteoma (not illustrated) is a compact osteogenic tumor, and *fibroosteoma* is a diffuse one. Both are slow-growing benign neoplasms; a conservative surgical approach is used when the tumors may lead to deformities.



Cyst of epiglottis (mirror view)



Fibrolipoma of vallecula



BENIGN TUMORS OF VALLECULA AND ROOT OF TONGUE (HYPOPHARYNX)

In the *vallecula* and *root of the tongue*, small connective tissue *tumors* of benign character may exist for a long time before they become large enough to cause solid-food dysphagia. Occasionally, the presenting complaint may be difficulty in breathing when the head is in certain postures; the primary reason for this is that these benign tumors are frequently pedunculated and compromise the airway when the tumor mass is dislodged by a change in position of the head. The tumors are smooth, soft, and covered by an intact mucosa. The most common of them is the retention *cyst of the epiglottis*, which is easily detected during a mirror examination. The cyst may be freely movable because of the pedunculated attachment to the mucosal surface of the epiglottis. Removal by forceps under indirect laryngoscopy is adequate.

A *fibrolipoma of the vallecula* may not be discovered until there is interference with normal breathing. The tumor mass is usually rounded, of a yellowish tinge, and covered by a smooth mucosa. The mass has a sessile attachment to the lingual surface of the epiglottis, which it displaces posteriorly, thereby overhanging the aditus of the larynx. The benign nature of the tumor is usually self-evident. Treatment is surgical excision of the lesion.

Neuroma of the vallecula (not illustrated) is rare but may attain a large size before becoming apparent. The symptoms vary with the size of the tumor and may result in dysphagia or difficulty in breathing.

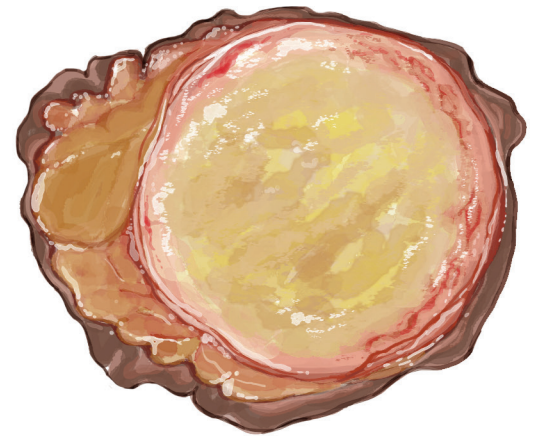
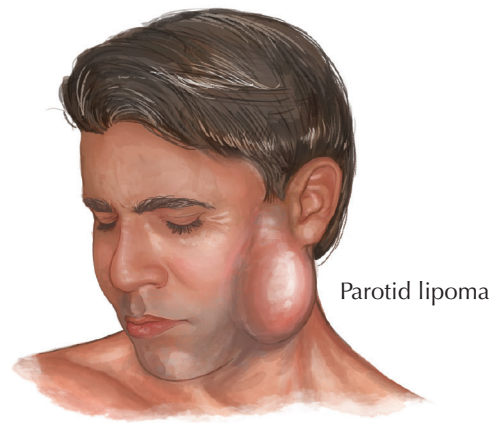
An *aberrant lingual thyroid gland* may be present for a long time before it is diagnosed. It makes its appearance as a smooth bulge in the posterior surface of the tongue, starting in the region of the foramen cecum and extending posteriorly to the lingual surface of the epiglottis. The mass presents as a smooth surface soft to the touch and covered by an intact mucosa. Some tumors may become so large that they interfere with respiration; tumor extension inferiorly and/or depression of the epiglottis into the laryngeal vestibule may be the reason. The diagnosis should always be entertained when a smooth tumor of the base of the tongue is encountered. The diagnosis is often made by exclusion. A thyroid scan with a radioactive iodine tracer demonstrated in the region of the mass will establish the diagnosis. Biopsy typically yields insufficient tissue because of the depth required to reach the aberrant thyroid tissue. If

the mass produces no symptoms, therapy is probably not indicated.

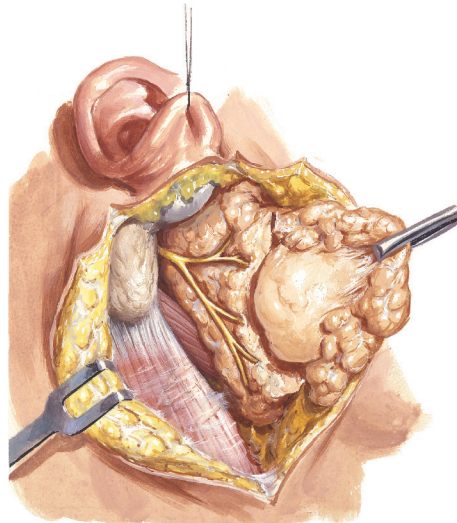
Microscopically, the aberrant lingual thyroid typically presents as a normally functioning thyroid gland, which should be left intact whenever possible. A thyroid scan will demonstrate the functional nature of the lingual gland. If the mass is so big that it endangers respiration, therapeutic doses of radioactive iodine suffice to cause a subsidence of the tumor and to create

a hypothyroid state, which must be treated accordingly. Adenomatous tissue, which can be found in the lingual thyroid gland and is also often found in the normally located thyroid, is best removed by surgical resection.

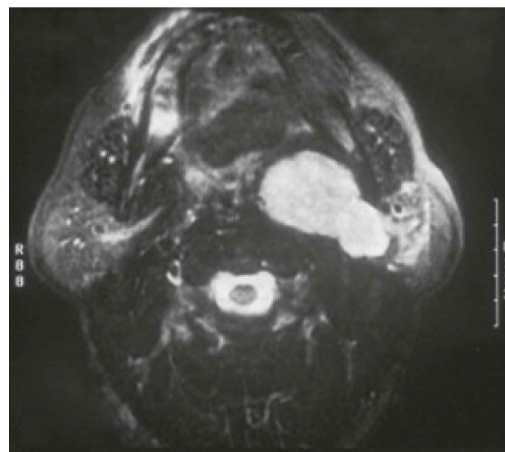
In the base of the tongue, other tumor masses may occur that require removal. Myoblastoma is a common finding and responds to surgical extirpation. Amyloid tumors of the tongue and chondromas have been described and are less amenable to therapy.



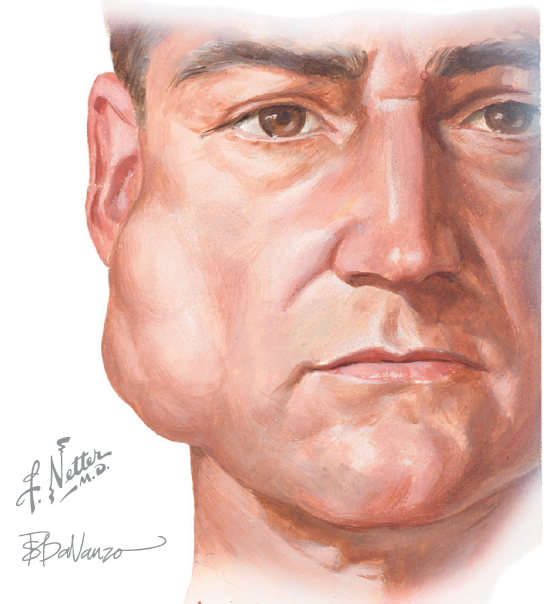
Gross appearance of pleomorphic adenoma



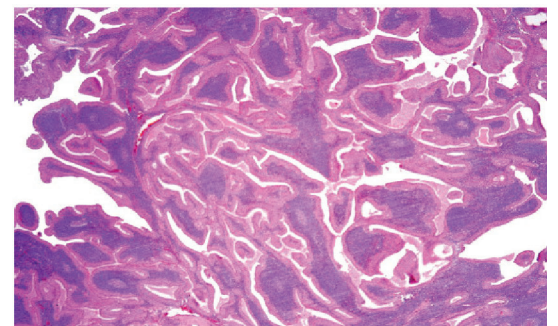
Tumors of parotid gland



Pleomorphic adenoma of parotid: high intensity signal on T2 weighted MRI (From Flint PW, Haugher BH, Lund VJ, et al. Cummings Otolaryngology–Head and Neck Surgery. Elsevier, Philadelphia, 2014.)



Benign mixed salivary gland tumor



Warthin tumor, low power. Papillary-cystic tumor associated with a dense lymphoid stroma. (From Thompson LDR. Head and Neck Pathology: Foundations in Diagnostic Pathology, Elsevier, Philadelphia, 2012.)

BENIGN TUMORS OF SALIVARY GLANDS

Pleomorphic adenoma, also referred to as a *mixed salivary gland tumor*, is the most frequently seen benign salivary gland neoplasm, accounting for 60% of such tumors. The most common site of origin is the parotid, followed by the minor salivary gland and submandibular gland. It has a female predominance in adults and a male predominance in children. The tumors are indolent, slow-growing, typically asymptomatic lesions. Most often, a tumor begins in the lower portion of the gland and gradually enlarges to present as an ovoid or rounded well-circumscribed mass that is typically encapsulated. When expanding into the depth of the parenchyma, the tumor tends to be hard and lobulated, causing thinning of the overlying skin. Facial nerve involvement may result from direct infiltration or through external pressure on the neural tissue. The tumor is composed of ductal epithelial and myoepithelial cells with morphologic features of spindle, plasmacytoid, epithelioid, stellate, or basaloid cells residing most often in a mucochondroidal mesenchymal stroma. Recurrent lesions following surgical excision are typically multinodular.

Basal cell adenoma is a result of a proliferation of basaloid cells in a solid, tubular, trabecular, or membranous pattern. The tumors are typically solitary, asymptomatic, and slow growing and arise from the parotid gland. Lesions are well circumscribed and can grow to 3 cm in diameter. The recurrence rate following surgical excision for all but the membranous variant is quite low.

Papillary cystadenoma lymphomatosum, typically referred to as a *Warthin tumor*, is the second most common salivary gland neoplasm, occurring primarily in the parotid gland. Warthin tumors, unlike other salivary gland lesions, have a strong association with tobacco use. These lesions are most often seen in white men in the sixth or seventh decade. The tumor is frequently multilobular and bilateral, and like other salivary tumors, it is slow growing, reaching 4 cm in diameter. It consists of a double layer of oncocytic epithelium within a dense lymphoid stroma arranged in a

papillary and cystic pattern. The lesions likely develop from salivary tissue intertwined with lymph nodes draining the parotid gland. The recurrence rate is up to 25% with surgical excision. Although malignant transformation is rare, squamous cell carcinoma or B-cell lymphoma may develop from the tumors.

Canalicular adenoma accounts for 1% of benign salivary gland tumors, with a preference for the minor salivary gland, specifically, the upper lip. It is most com-

monly seen in African American women in their seventies. The lesions are typically firm, slow growing, and solitary, reaching up to 2 cm in diameter. On gross inspection, the lesions are well-circumscribed, solid, or cystic pink/tan nonencapsulated masses. Histologically, the tumor consists of long, single-layered strands or tubules of cuboidal to short columnar cells within a loose, lightly collagenous stroma. Treatment is surgical excision of the lesion. Recurrence is rare.

BENIGN TUMORS OF FAUCES AND ORAL PHARYNX

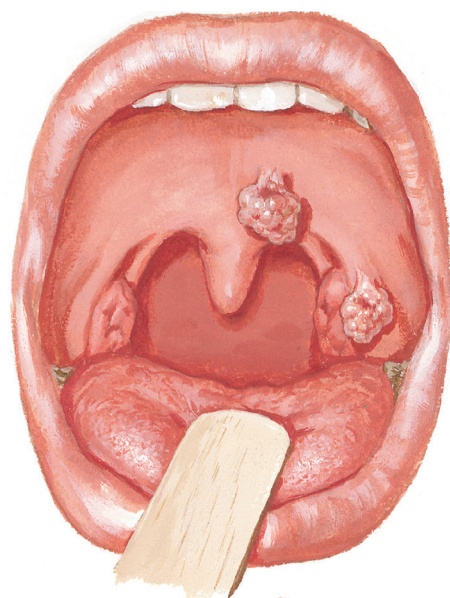
The great majority of benign tumors of the oral pharynx are of connective tissue origin; small epithelial *papillomas of the tonsillar pillars and soft palate*, though not rare, are less often seen, because they are generally symptom-free and are detected only accidentally on routine examination. The small papillary masses can be removed at the base with a forceps; after cauterization, they rarely recur.

Squamous papilloma is a common benign nonneoplastic lesion of the oropharynx. It consists of nonkeratinized squamous epithelium within a fibrovascular connective tissue stroma. It is seen in association with human papillomavirus serotypes 6 and 11. Although it can be found on all intraoral mucosal sites, it has a predilection for the hard and soft palate and uvula. Verruca vulgaris, the common wart, can be seen in the same oropharyngeal regions and is also associated with human papillomavirus infection but with serotypes 2 and 4.

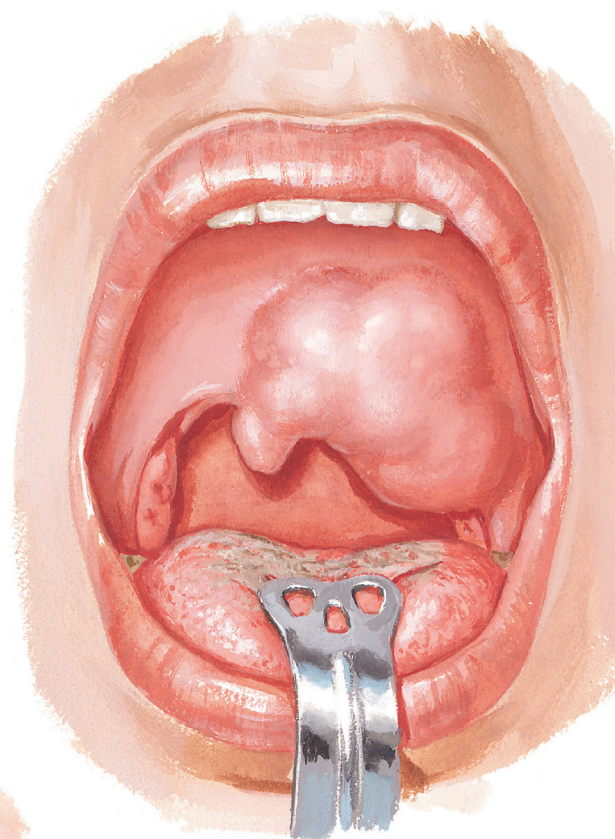
Small adenomas of the soft palate and the posterior pharyngeal wall are seldom seen and are best treated by excision.

The more frequent types of tumors are the sessile, connective tissue tumors of angiomatous origin. *Hemangioma* of the oral pharynx is usually congenital but may go unnoticed until later in life. The bluish purple discoloration of the tumor through the overlying distended mucosa is characteristic and permits the diagnosis without further microscopic examination. The mass is soft and collapsible on pressure. Many of these tumors are symptom-free and only rarely do they produce bleeding. Hemangiomas of the pharynx are occasionally associated with similar lesions on the lip, tongue, or cheek and elsewhere in the gastrointestinal tract. No therapy is indicated unless the lesions become large and symptomatic. Surgical excision is the treatment of choice.

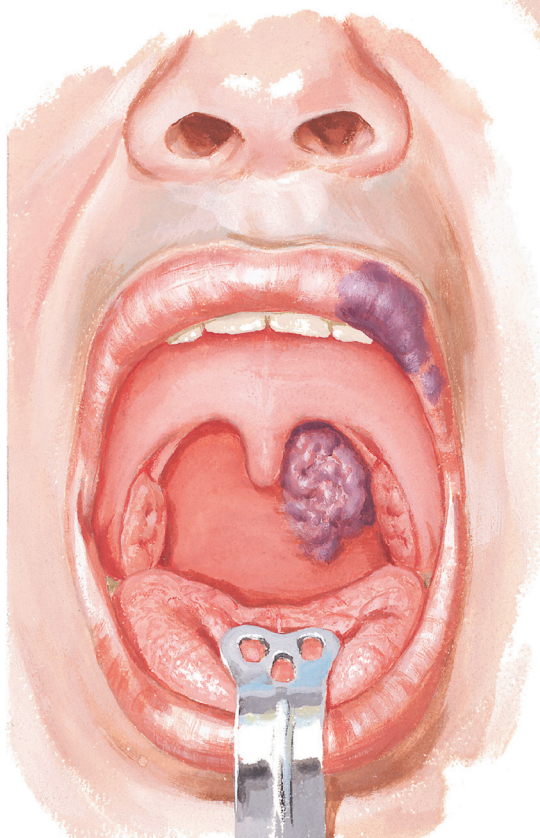
Mixed tumors of the pharyngeal wall present as smooth, rather firm, submucosal bulges. They are occasionally seen in the retrotonsillar region behind the soft palate, on the posterior pharyngeal wall, or in the substance of the soft palate itself. Diagnosis may be made by needle biopsy. More frequently, excisional biopsy of the whole tumor with a safe margin of mucosa on the free edges establishes the diagnosis and provides surgical excision of the lesion. Mixed tumors have a tendency to recur unless they are widely excised. If the tumor is broken or incompletely removed, recurrence is common.



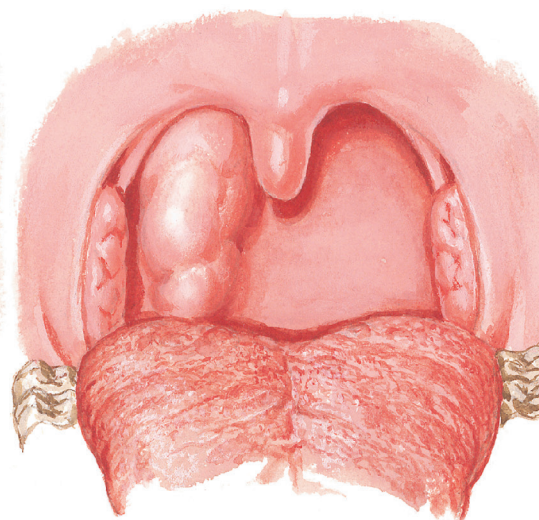
Papillomas of soft palate and anterior pillar



Mixed (salivary gland) tumor of pharyngeal wall



Hemangioma of pharyngeal wall



Neurofibroma of pharyngeal wall

Neurofibroma of the hypopharynx presents as a sessile, nodular, submucosal tumor frequently extending in a linear fashion along the posterior or lateral pharyngeal wall. These tumors may be associated with diffuse neurofibromatosis. They are encapsulated tumors that protrude into the hypopharynx. Diagnosis may be suspected from aspiration biopsy, but excisional biopsy with a wide margin of mucosa is more reliable.

Other less frequent types of tumors of connective tissue origin, occasionally seen in the oral pharynx,

include lipomas, myoblastomas (especially on the posterior aspect of the tongue), and fibromas of the pharyngeal mucosa. Rarely, a myoblastoma may develop as a result of a trauma and submucosal hemorrhage. These tumors, characterized by polygonal cells with highly granular cytoplasm, can be felt as a deep mass below the mucosa. They are not as firm as carcinoma and have no tendency to ulcerate. All these neoplasms are best treated by local excision, which both establishes the diagnosis and effects a cure.

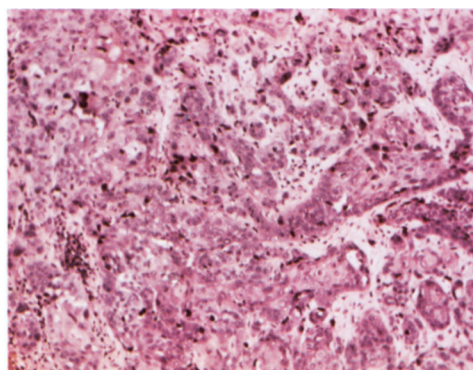
F. Netter M.D.

MALIGNANT TUMORS OF ORAL CAVITY AND OROPHARYNX

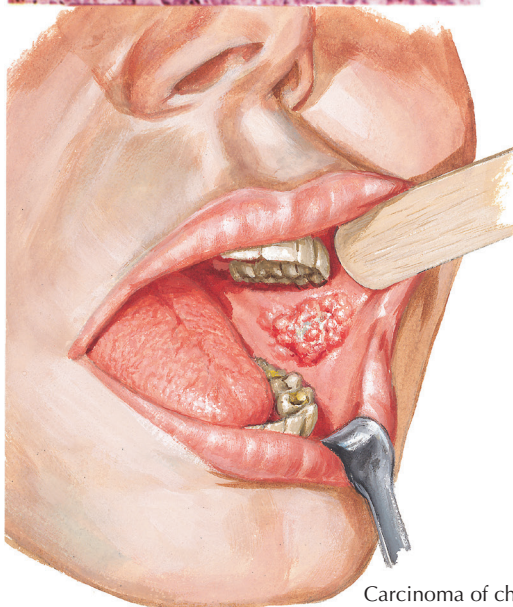
Squamous cell carcinoma (SCC), an epidermoid cancer, is the most common malignancy in the oral cavity and oropharynx. It arises from the epithelial lining of the oral cavity in order of decreasing frequency in the lips, tongue, floor of the mouth, gingiva, and palate. In the oropharynx, it arises most often from the palatine tonsillar crypts. Although there are similarities in squamous cell carcinogenesis in the oral cavity and oropharynx, significant clinical and biologic differences also exist, suggesting that SCCs in the two regions are two separate disease entities. Both oral cavity and oropharyngeal cancers have a male predominance, and both are rarely seen before the age of 50. A striking difference between the two malignant processes is the declining incidence of SCC in the oral cavity and the rising incidence of it in the oropharynx. Tobacco is the most significant risk factor for the development of oral cavity SCC. Alcohol has a synergistic effect with tobacco as a carcinogen in this process. Betel nut chewing, radiation exposure, vitamin deficiencies, and environmental and occupational exposures are atypical risk factors in the development of SCC. Although tobacco remains a risk factor for the development of oropharyngeal cancer, human papillomavirus infection, specifically with serotype 16, is likely the most important causative agent in the development of SCC of the oropharynx.

Oral cavity cancer typically begins with a malignant precursor of leukoplakia or erythroplakia. In leukoplakic lesions, the tendency toward malignant growth is high if the cells of the prickle cell layer show disorientation with dyskeratosis. Fissuring and papillomatous formation are clinical danger signs during the transformation process of the premalignant lesion. In contrast, a precursor lesion is not typically seen with oropharyngeal SCC. Dysphagia, odynophagia, otalgia, and weight loss are clinical presentations shared by both oral and oropharyngeal SCC. Dentition problems and oral bleeding are typical of oral SCC, and obstructive sleep apnea and the presence of a neck mass are frequent findings in oropharyngeal SCC. The gross appearance of SCC varies from grayish white, nondescript, thickened mucosa consistent with its precursor leukoplakia to large flat, ulcerated lesions or bulky fungating masses with or without local invasion. Dysplastic epithelial changes occur early in the disease course. Basement membrane compromise is indicative of invasive disease, allowing for perineural and lymphovascular invasion. Histologically, most oral SCC lesions demonstrate squamous differentiation, with nests of cells with pink cytoplasm, intercellular bridges, and keratin pearls with a desmoplastic stroma. Oropharyngeal SCC demonstrates "blue cell" morphology with scant cytoplasm and hyperchromatic nuclei with high mitotic activity and little to no keratinization. Regional or cervical lymph node spread is frequently seen with oropharyngeal SCC and much less often with oral SCC. In tumors associated with human papillomavirus infection, the overall prognosis is much better for oropharyngeal SCC than for oral SCC. Treatment for both diseases includes a "cocktail" of irradiation and chemoradiation and/or surgical resection.

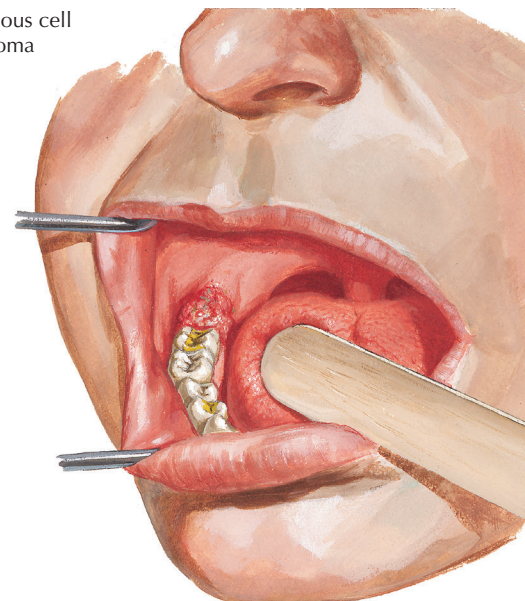
Luetic glossitis, considered a premalignant lesion, is an oral manifestation of syphilis, which presents as diffuse lingual atrophy with a loss of papillae. *Kaposi sarcoma* is an endothelial malignancy seen in the oral cavity, primarily in patients with AIDS. Rarely, it can be found



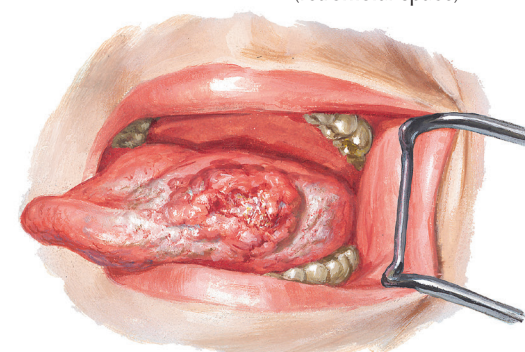
Squamous cell carcinoma



Carcinoma of cheek



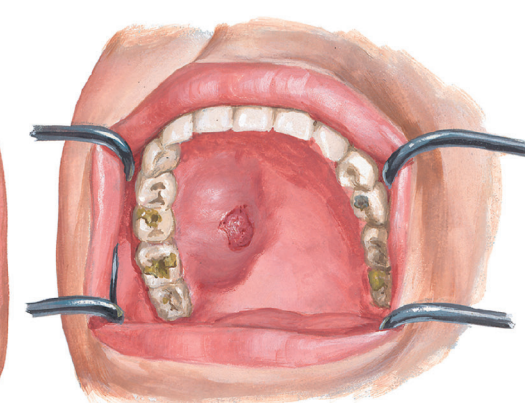
Carcinoma of gingiva (retromolar space)



Carcinoma of tongue (on leukoplakia)



Lymphosarcoma of palate and gingiva



Adenocarcinoma of palate

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in older men of eastern European or Mediterranean descent; in patients from endemic areas of Africa, specifically Bantu children from South Africa; and in immunosuppressed individuals, particularly transplant recipients. The clinical subtypes differ according to the epidemiologic group affected. The most common site in the oral cavity is the palate, followed by the gingiva and dorsal surface of the tongue. The appearance of the lesion depends on the point in time that it is seen during the disease course. Early lesions are flat, red, and asymptomatic, and late lesions are larger, darker, and

raised, with ultimate progression to large nodular lesions that ulcerate, bleed, and are painful. The incidence of this lesion has decreased dramatically with the widespread use of highly active antiretroviral therapy (HAART).

Lymphosarcoma, as well as other varieties of lymphoblastomas, may be observed occasionally in the oral cavity. The tumor originates from lymphoid tissue in the submucosa, especially the palate and pharynx. Typical features of this type of tumor are rapid growth and early local and regional lymph node metastases.

MALIGNANT TUMORS OF SALIVARY GLANDS

Although most tumors of the parotid gland are benign, approximately 20% are malignant, most often primary malignancies and less often malignant transformations of mixed tumors, adenomas, and cysts.

Adenocarcinoma is rare in the oral cavity but is a primary tumor of the major salivary glands, particularly the parotid. In the oral cavity, it develops from embryonic epithelium associated with small mucous glands, arising chiefly in the palate. It begins as a deep-seated nodule beneath the mucosa, which may break through the surface and ulcerate at a late stage. Adenocarcinoma accounts for almost 20% of all salivary gland carcinomas, with up to 60% affecting the major glands, primarily the parotid.

Salivary duct carcinoma is an aggressive adenocarcinoma representing 9% of malignant salivary tumors that almost universally affect the major glands, particularly the parotid. Unlike most salivary gland tumors, there is a marked male predominance, with a wide age range from young adults to the elderly. As pictured here, it presents as a hard, nonencapsulated swelling, beginning in the uppermost part of the gland or in the retromandibular lobe and growing rapidly to distend the face. The intensity of pain may be severe from pressure on the sensory nerves. The adjacent tissues are infiltrated, and the mass appears, on palpation, to be implanted on the ramus of the mandible, with fixation of the overlying skin. Histologically there may be a reproduction of ducts or acini, or a composition of strands and groups of mucus-producing cells enclosing lumenlike structures (*cylindroma*) embedded in a mucoid or hyaline degenerative stroma. The tumor is solid, is white-gray or tan, and contains cystic, necrotic, and hemorrhagic components with suggestions of a preexisting pleomorphic adenoma. It presents as a rapidly growing mass with ulceration and frequent facial nerve paralysis, with associated regional lymph node and distant metastatic spread to lung and bone. As the most aggressive salivary gland tumor, the 5-year survival rate is less than 30%.

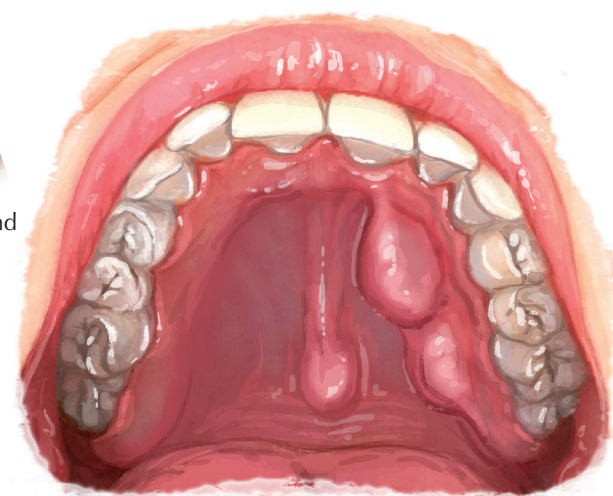
Polymorphous low-grade adenocarcinoma is almost exclusively seen in the minor glands and accounts for about 20% of intraoral malignant salivary tumors primarily involving the palate. There is a female predominance occurring most commonly in the sixth to eighth decade. Lobular, solid-nest and cribriform and ductlike architectural patterns are seen with the tumor. The prognosis is excellent, with a low risk of recurrence following surgical excision.

Carcinoma ex pleomorphic adenocarcinoma accounts for 4% of all salivary tumors and 12% of salivary malignancies. It is seen in the minor, major, and submandibular glands, with a predilection for the parotid. There is an equal gender distribution, and it occurs primarily in the sixth to seventh decade. The clinical presentation is of a long-standing mass, with rapid enlargement or recurrence of a previously resected pleomorphic adenoma. The tumors are of variable size but can become larger than 20 cm. The prognosis depends on the aggressiveness of the tumor grade.

Mucoepidermoid carcinoma is the most common salivary gland tumor (12% to 29% of tumors), with the majority occurring in the major gland, particularly the parotid. There is a female predominance, with most occurring in the fifth decade. Intraoral lesions are typically bluish red and fluctuant, mimicking a mucocele or vascular lesion. In the parotid, the lesions are typically circumscribed encapsulated cysts containing brown or gray



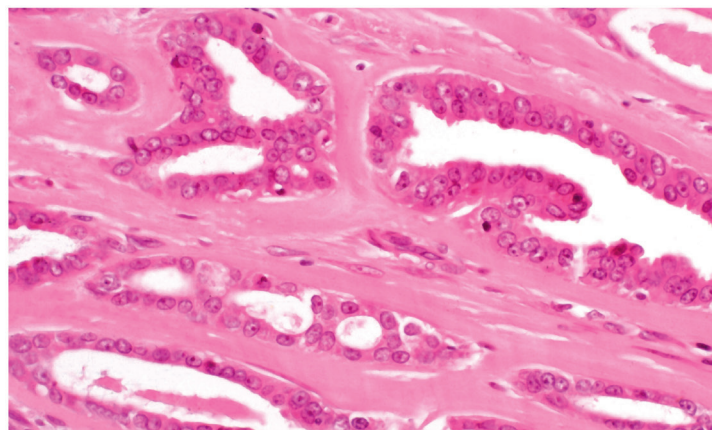
Mucoepidermoid carcinoma in parotid gland



Mucoepidermoid carcinoma on palate



Gross appearance of mucoepidermoid carcinoma



Adenocarcinoma of salivary gland (From Thompson LDR. *Head and Neck Pathology: Foundations in Diagnostic Pathology*, Elsevier, Philadelphia, 2012.)

mucous fluid and are lined by intermediate, mucous, or epidermoid cells. With increasing size there is a risk of rupture that can allow tumor cell contamination into surrounding structures. Low-grade tumors typically are cystic and have abundant mucocytes, minimal atypia, or low mitotic activity; the prognosis is excellent following surgical resection. High-grade tumors are much less common and show cytologic atypia, high mitotic activity, necrosis, and neural invasion. Despite surgical intervention, the mortality rate remains about 50%.

Acinic cell carcinoma accounts for about 6% of salivary gland tumors, with most occurring in the parotid gland.

It is a malignant epithelial tumor with serous acinar differentiation containing cytoplasmic zymogen secretory granules. Female predominance is seen, with a wide age spread from the twenties to the seventies. This is the second most common salivary gland malignancy in children (mucoepidermoid tumors are the most common). Its growth is variable and may take weeks to decades, with most tumors being slow growing. The tumor typically presents as a rubbery firm, circumscribed, oval, or round mass that is either mobile or fixed. Recurrences following surgical excision are seen in about a third of individuals.

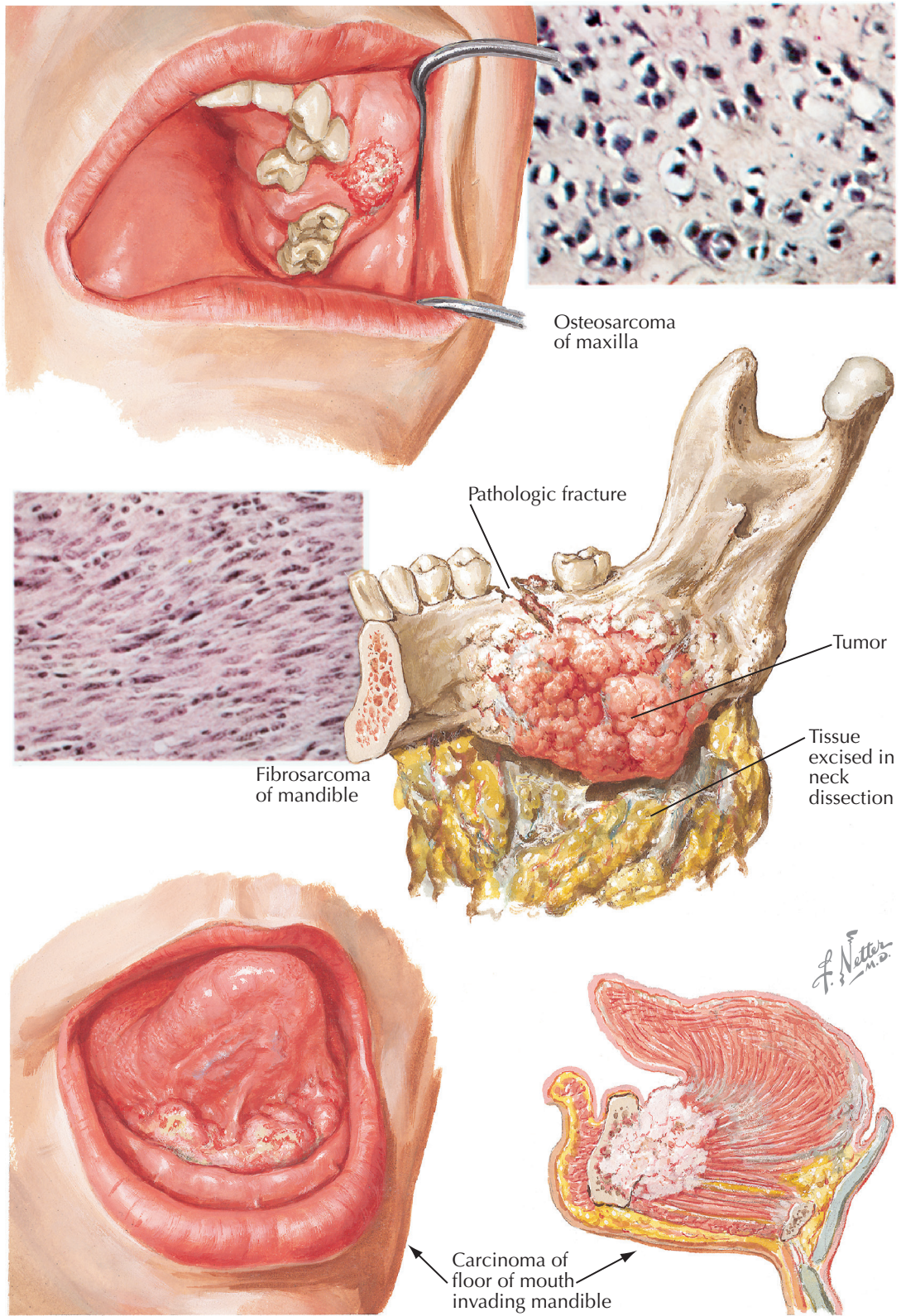
MALIGNANT TUMORS OF JAW

Malignant tumors involving the jawbones are nearly always epidermoid carcinomas, which are formed from peripheral epithelium and invade the bones secondarily. Malignant transformation of a benign neoplasm, particularly of a mixed tumor of salivary tissue, is sometimes seen. Metastases of primary carcinoma of the thyroid, breast, or prostate to the jaws via the bloodstream are very rare, and so are malignant primary tumors of odontogenic, osteogenic, or other origin.

Though *osteogenic sarcoma* is the most common and most malignant of bone tumors, only 2% to 3% of cases appear in the jawbones. Trauma is believed to play a role in its etiology, as evidenced by clinical histories and experimental production in animals. It is a solitary growth, which differentiates it from various tumors of nonosteogenic origin (e.g., endothelioma, multiple myeloma). The maxillary tumor illustrated has caused wide, mottled destruction of bone, as revealed by radiographic findings. The classic “sun-ray” pattern seen in the long bones is seldom appreciated in the jaws, although new bone formation may be noted. The swelling can involve the entire maxilla and portions of the palate, with invasion into the antrum. Pain, paresthesia, swelling, tenderness, and displacement of teeth, with disturbed mastication, are associated symptoms. Hematologic metastasis can be an early phenomenon.

The histopathologic picture shows immature cells, which are pleomorphic and hyperchromatic, with some admixture of stroma, myxomatous tissue, cartilage, and osteoid tissue. Pathologic descriptions sometimes refer to osteolytic, osteoblastic, and telangiectatic (vascular) types. The osteoblastic variety tends to grow more slowly than the vascular type.

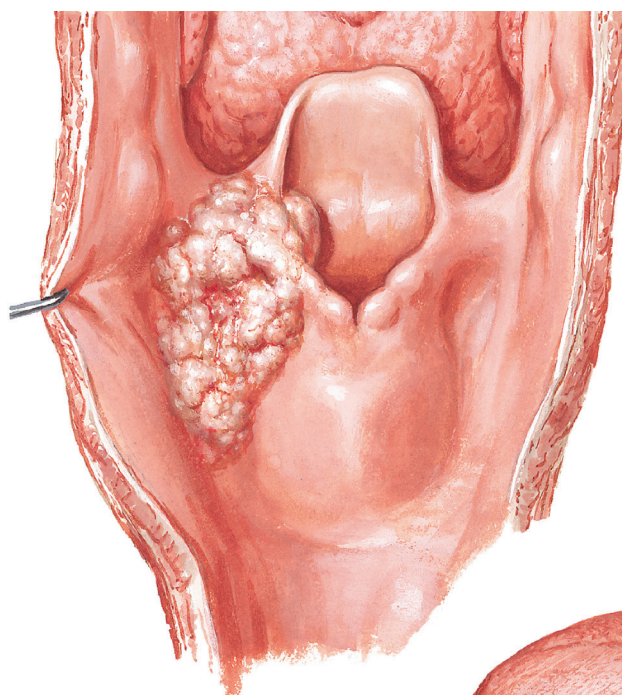
Fibrosarcoma may be formed peripherally and invade the jaws, or centrally from tissues of the tooth, germ or other mesenchymal enclaves, or connective tissue elements of the nerves and blood vessels. In the case of rapidly advancing osteolytic lesions, clinical recognition is usually delayed until loosening of the teeth, encroachment on the antrum or nose, or perforation of the cortical plate has occurred. No evidence of periosteal activity is noted, as is sometimes the case with osteosarcoma. Frequently, proud flesh in the socket of an extracted tooth is the first sign of an underlying malignancy. In the *mandibular tumor* chosen for illustration, pathologic fracture was caused by the widespread destruction of medullary bone. The tumor mass has perforated the lingual wall of the mandible, with invasion of soft



tissues in the floor of the mouth and neck. Radiographic examination showed a blurred, diffuse osteolytic area, denoting an invasive rather than an expansile growth. The microscopic picture reveals spindle-shaped cells, with anaplasia and varying amounts of intercellular collagenous tissue; in the rapidly growing forms, a plump cellular shape with frequent mitoses is seen, but little intercellular material is present.

Carcinoma invading the mandible is illustrated in a lesion of the anterior floor of the mouth. The tumor here

is a grade III malignancy, causing early infiltration of cortical bone, with progress along the haversian canals and destruction of a large portion of cancellous bone. At the same time, extension occurs through the lymph channels to involve the submandibular and cervical nodes, as well as the soft tissues contiguous to the tumor. The base of the tongue has become fixed and immobile. A fungating tumor mass is observed in the floor of the mouth, which is secondarily infected and extremely painful, with a foul exudate and odor.

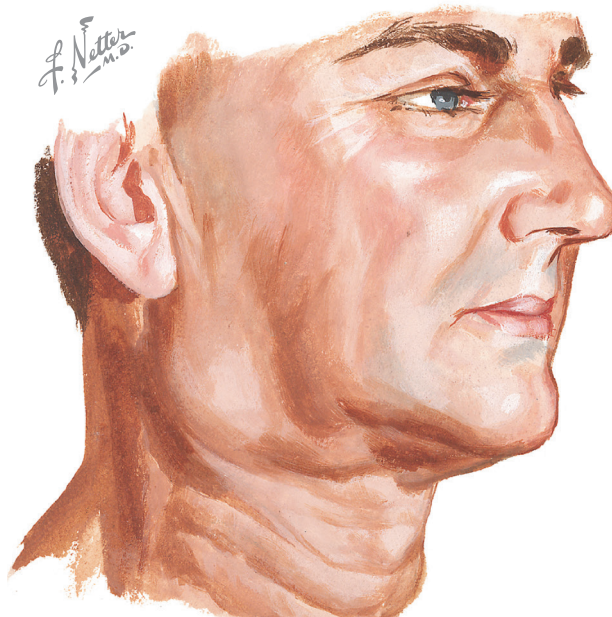


Carcinoma of piriform recess

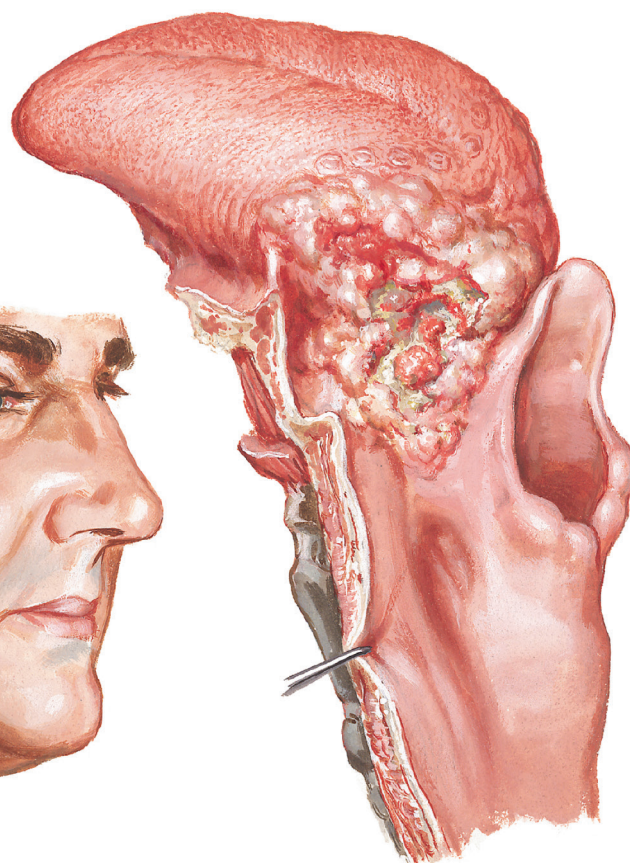
MALIGNANT TUMORS OF HYPOPHARYNX

Malignant tumors of the hypopharynx are predominantly of epithelial origin. *Squamous cell carcinoma of the root of the tongue* presents with pain on swallowing, otalgia, discomfort in the throat, and, finally, difficulty in breathing. The ulcerative, infiltrative form produces early cervical node metastasis, but the proliferative type presents as a bulge on the root of the tongue and is readily visible and easily palpable. These lesions are typically quite advanced before producing symptoms sufficient to bring the patient to the physician. Palpation of the base of the tongue will often permit recognition of a firm mass, even when it is not detectable on basic oral examination. Many of these carcinomas are of the immature or undifferentiated type, explaining their tendency to early metastasis. The tumor may extend into the vallecula and displace the epiglottis toward the laryngeal lumen, causing some hoarseness and, occasionally, difficulty in breathing in the reclining position. Pain on swallowing usually prompts the patient to seek medical advice. On mirror examination, an ulcerative growth may be visible, which is frequently covered with debris and whitish exudate. The tumor may extend into the tonsillar pillars and floor of the mouth. Although usually confined to one side, it may extend across the midline. Grasping and extending the tongue will expose the posterior third of the tongue. Biopsies of the lesion are necessary to obtain a pathologic diagnosis; the method for obtaining the biopsy material varies with the prominent tumor location.

Carcinoma of the piriform fossa is an extrinsic laryngeal lesion. The tumor may arise on the medial wall of the piriform fossa and extend onto the aryepiglottic fold and epiglottis, or it may have its origin on the lateral wall of the piriform fossa and extend onto the lateral wall of the pharynx and down into the mouth of the esophagus. These lesions produce symptoms only in a late stage of the disease. The vocal folds are not compromised, and hoarseness is a relatively late symptom.



Enlarged cervical node (often initial symptom in malignancies of tonsil, fauces, and pharynx)



Carcinoma of root of tongue

Dysphagia may also occur only late in the course because the pathway left free at the opposite piriform fossa is usually adequate for deglutition. The first symptom of the presence of this lesion may be the appearance of a cervical node on the same side of the neck. Diagnosis is best made by mirror examination followed by biopsy, which can be obtained by direct or (most often) indirect laryngoscopy. Tomography of the larynx, especially in the anterior-posterior position, will often show an obliteration of the piriform fossa on

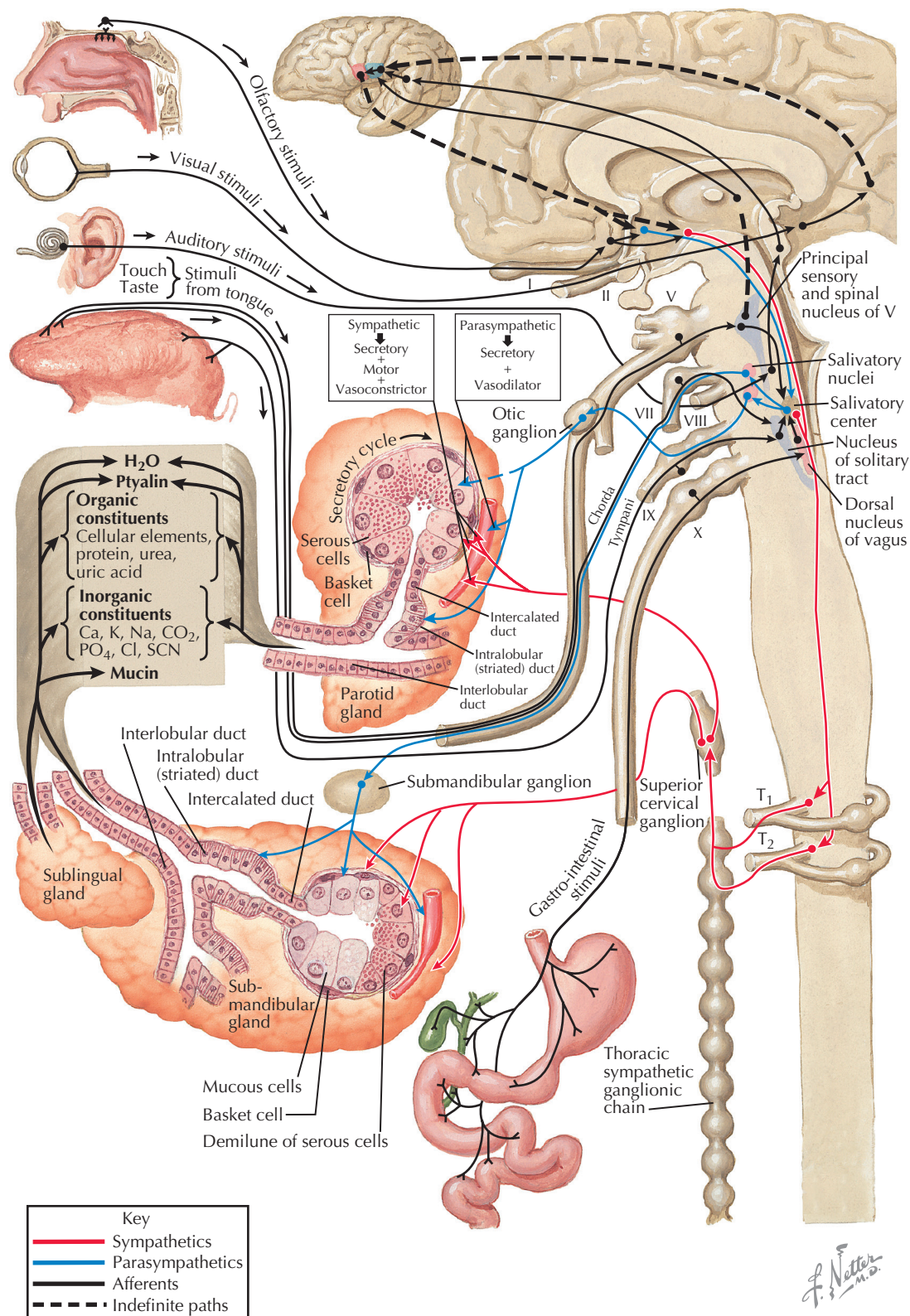
the involved side. The lesions are invariably squamous cell carcinomas, with a high percentage of undifferentiated or immature cell types. Irradiation and surgical therapy result in similar rates of control and survival for many head and neck locations. The therapeutic choice depends on the site and surgical accessibility of the lesion, the hoped-for functional outcomes (speech and voice production, swallowing, and airway protection), and the types of morbidity associated with each modality.

SALIVARY SECRETION

Stimulation of areas in the *premotor region of the cortex cerebri* (in the vicinity of the masticatory center) and in the *hypothalamus* evokes salivation. The neural pathways from these nuclei and the sympathetic and parasympathetic innervation of the salivary glands have been described in Plate 2-13.

During the resting or recovery phase, when no secretory stimuli are acting, granules of mucinogen, the precursor of mucin, are formed in the mucous cells, and granules of zymogen, the precursor of amylase (ptyalin), are formed in the serous or demilune cells. Extrusion of these substances, together with other components, into the lumen of the alveoli and into the ducts is principally regulated by neural pathways and gastrointestinal hormone secretion. The *parasympathetic nerves* supply the mucin-secreting cells and intralobular duct cells, and the *sympathetics* govern the serous cells and myoepithelial, or "basket," cells, which lie between the basal membrane and the secretory cells and are presumed to account for the contractile action that permits a gush of saliva. The quantity and composition of saliva are adapted to the nature of the agent that stimulates, chemically or mechanically, the nerve endings (V and IX) of the oral mucosa (unconditioned reflex). Thus, edible substances generally produce a viscid saliva, rich in mucin and enzyme. Inedible substances such as sand evoke a watery secretion. Acid material stimulates saliva with buffering (high protein content) and diluting properties. Milk, in contrast to other fluids, evokes a copious flow of saliva, rich in organic material. These unconditioned reflex responses do not depend on any learning process and have been elicited experimentally in decerebrated animals. The conditioned reflexes, on the other hand, are manifested by the flow of saliva in association with the thought or sight of food and with events the individual has learned to relate to food, such as the sound of a tuning fork in Pavlov's famous experiment with dogs.

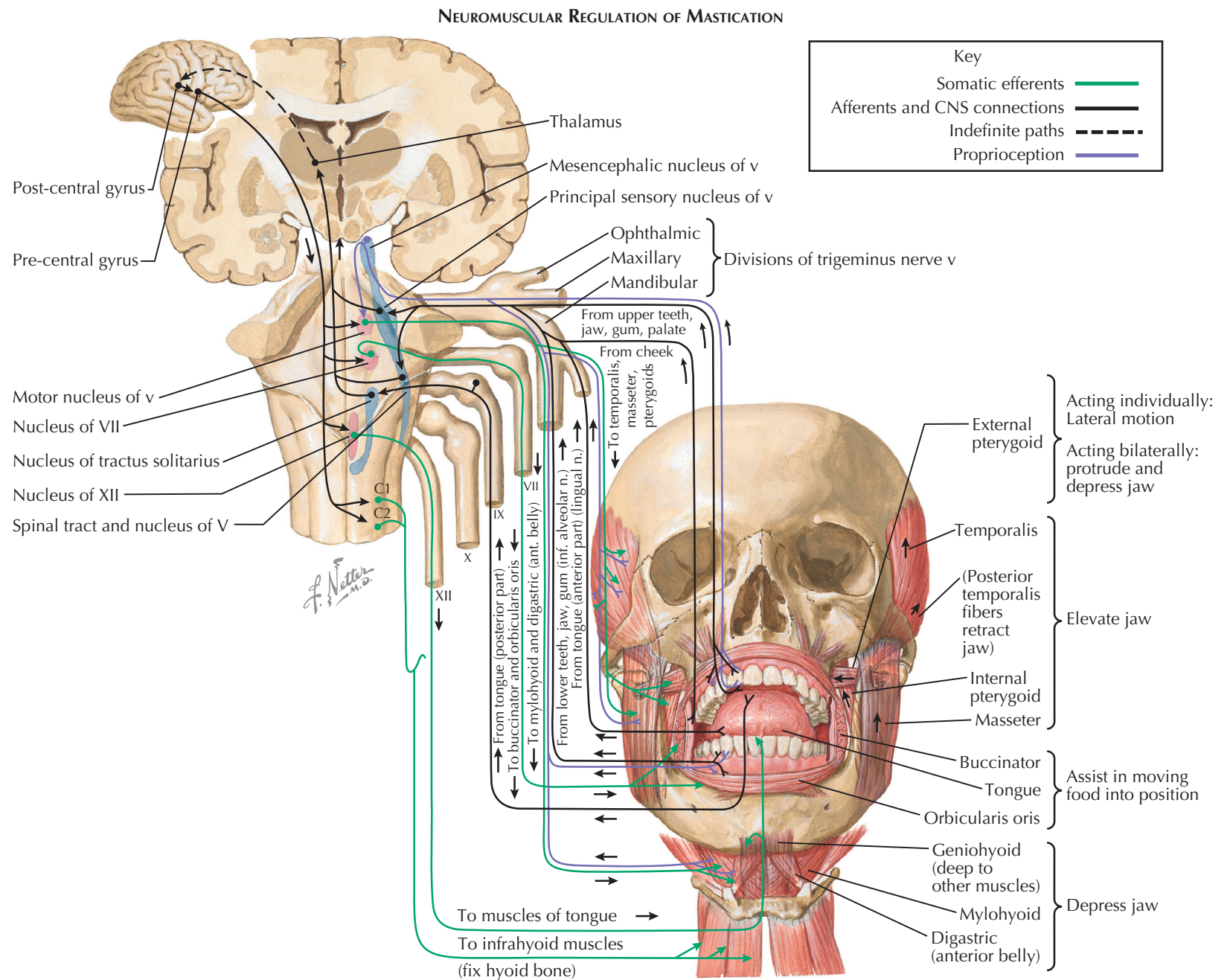
The total amount of saliva secreted per day is estimated at 1000 to 1500 mL. The specific gravity varies from 1003 to 1008 and the pH from 6.2 to 7.6. Resting saliva is usually acidic; freely flowing saliva is usually alkaline. The viscosity varies with the type of stimulus and the rate of flow. The *parotid gland* forms a watery fluid containing protein, salts, and ptyalin but no mucus. The *sublingual gland* is predominantly mucous, whereas the *submandibular gland* is intermediate, though predominantly serous. Saliva is hypotonic, and its osmotic pressure increases as the flow rate increases. The only salivary enzyme, *amylase (ptyalin)*, is produced by the parotid and submandibular glands and converts



starch into dextrins and maltose at a pH range of 4.5 to 9 (optimum 6.5). Ptyalin is inactivated at a pH below 4.5 and destroyed by heating to 65°C. Other *organic constituents* include cellular elements from the buccal mucosa and the glands, urea, uric acid, and traces of urease. The *inorganic constituents* consist of the anions Cl^- , PO_4^- and HCO_3^- and the cations Ca, Na, and K. The ratio of the last two in the saliva mirrors their presence in the blood serum. Present in the saliva is also a small amount of thiocyanate, which acts as a coen-

zyme that can activate ptyalin in the absence of NaCl. The saliva of smokers is relatively rich in potassium thiocyanate (KCNS).

Saliva has a cleansing action that plays a significant role in oral hygiene, but the salivary glands play a regulatory role in the homeostasis of water balance through negative and positive feedback loops. The glands stop secreting saliva whenever the body fluid content falls to a low level, resulting in dryness of the oral mucosa, thereby stimulating the sensation of thirst.



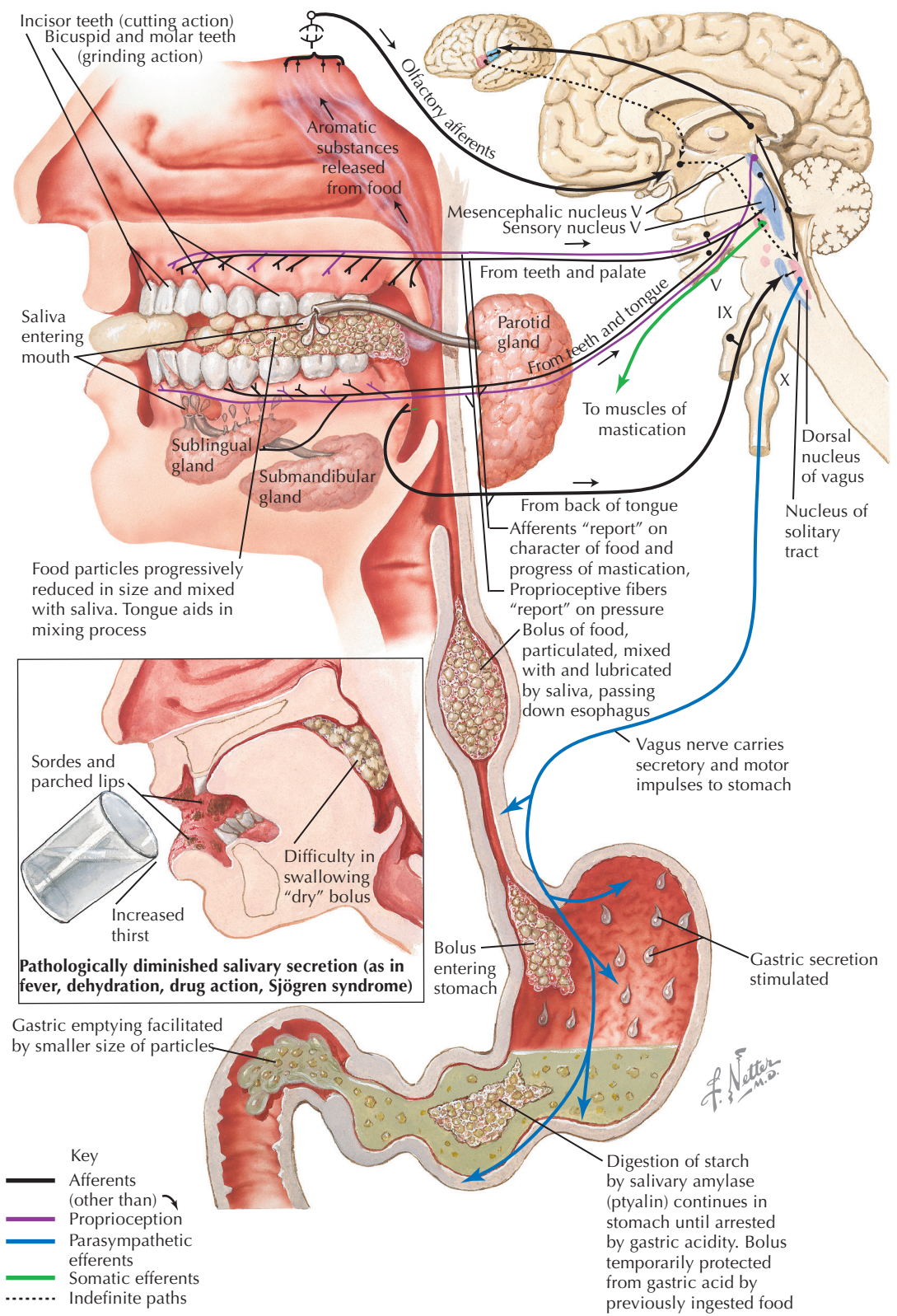
MASTICATION

All muscles involved in the act of mastication are striated, that is, voluntary; the neural regulation for the activity of the masticatory muscles originates in the inferior medial portion of the motor cortex, whence projections pass via the pyramidal tract to the pons to coordinate the motor nuclei of the nerves supplying the muscles of mastication. The complex movements of these muscles are centrally integrated, and coordination is aided by the impulses carrying sensation from the teeth and mucosal surface of the mouth, as well as proprioception from the muscles themselves. The proprioceptive pathways from the tooth sockets lead to the principal mesencephalic sensory nucleus (the only sensory root that has its cells of origin within the central nervous system) and thence to the motor nucleus, effecting control of the masticatory pressure and preventing the breaking of teeth.

Mastication begins with the cutting of the food by the incisor teeth and continues by bringing food in position between the grinding surfaces of the molars and premolars. The muscular forces of the tongue and cheek are also required in the act of grinding and mastication. The mandible is alternately elevated (masseter, temporal, internal pterygoid muscles) and depressed (digastric, mylohyoid, geniohyoid), and moved forward (external pterygoid) and backward (lower fibers of temporal) and from side to side (external pterygoid and elevators of the opposite side). The strength with which this grinding is performed may be appreciated by the fact that the molars have been shown to exert a biting force as high as 270 pounds. The primary purpose of mastication is to facilitate deglutition by reducing the size of the food particles and lubricating them with saliva. How much chewing is required to accomplish this depends on the type of food, the amount taken into the mouth at one time, the strength of the bite, the

intensity of hunger, and other factors. Ordinarily, by the time food is swallowed, most of it has been reduced to particles less than 2 mm in diameter. The largest particles usually do not exceed 12 mm. The nerve endings in the mouth sense the size of the particles that form the bolus and determine when the latter is ready to be swallowed. The efficiency of this function is such that rarely does a bolus become lodged in the normal esophagus.

Mere facilitation of swallowing is, however, not the only result of mastication. Thorough chewing also aids digestion. The prolonged contact of tasty food with the oral mucosa increases the cephalic (psychic) phase of gastric secretion, preparing the stomach for further grinding and propulsion of food into the duodenum. The greater the reduction in particulate size, the greater is the surface of ingested food, and the more readily is it exposed to both salivary and gastric enzymes. Reduction of particle size also facilitates gastric evacuation.



MASTICATION (Continued)

An important aspect of thorough mastication relates to the salivary secretion that it stimulates. Besides the diluting and lubricating effects of the saliva, its solvent action improves the taste and thereby further enhances the cephalic phase of gastric secretion. A copious flow permits more complete digestion of starches in the stomach before the bolus is penetrated by the gastric acid, which inactivates amylase (ptyalin). With diminished salivary secretion, termed *xerostomia* or *ptyalism*, as occurs in conditions of dehydration or fever or in the presence of Sjögren syndrome, all these effects are lost, and mastication is rendered extremely difficult. Certain agents, such as quinine, sympatholytics, and, particularly, anticholinergic drugs, inhibit salivary secretion and may produce undesirable effects on digestion. The opposite disturbance, excessive salivary secretion, called *amylasemia* (*ptyalism*) or *sialorrhea*, may result from a local irritation (jagged edges of teeth, poorly fitting dentures, dissimilar metals in fillings, lesions such as canker sores or stomatitis) or as a reflex of visceral disease. When extreme, the loss of the secreted fluid may lead to dehydration. Sialorrhea of a degree not clinically manifest has been observed in association with gastric hypersecretion in ulcer patients.

The most common disturbance of mastication probably is that resulting from the absence of teeth. Edentulous individuals attempting to eat food that requires effective chewing may swallow particles large enough

to tax the triturating action of the stomach. The same holds true for ill-fitting dentures. Thus, faulty mastication should be seriously considered as a cause of indigestion in an edentulous patient. Inadequate mastication resulting from poor dentition is typically a primary reason for esophageal food impactions and tracheo-bronchial aspiration. Loss of function of the buccinator and orbicularis oris muscles, as occurs in central or peripheral paralysis of the facial nerve, usually results

in the pocketing of food between the teeth and the adjacent lips and cheek, and thereby interferes with mastication on the affected side. Inability to chew food thoroughly may be one of the early signs of myasthenia gravis. Mastication is the initial step in propelling the food bolus to the pharynx for esophageal transfer. With poor dentition, this step cannot be completed properly, and these individuals can develop nutritional deficiencies, weight loss, and an overall reduced quality of life.

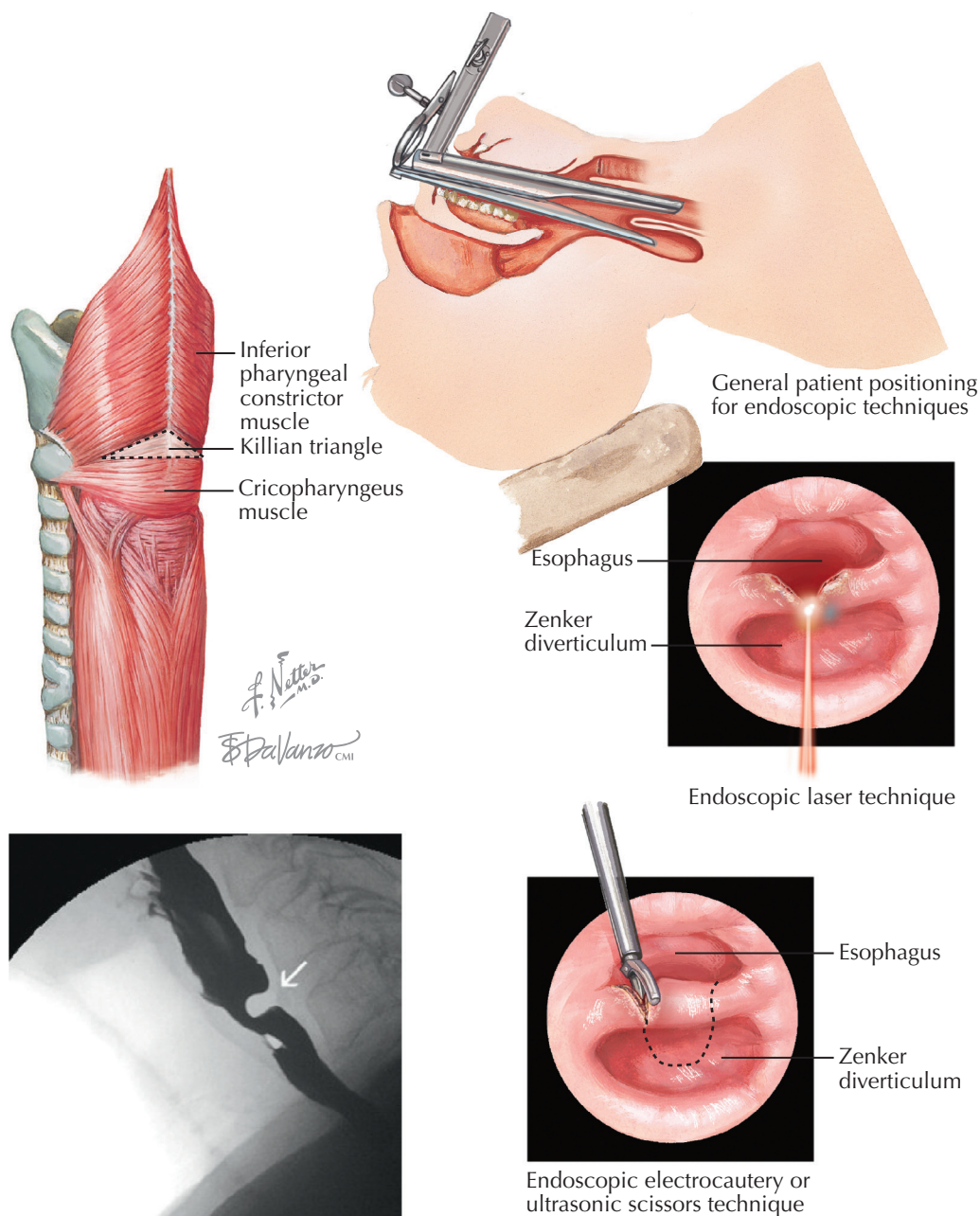
FUNCTIONAL DISORDERS THAT LEAD TO STRUCTURAL ISSUES

Oropharyngeal dysphagia is an abnormality in the proximal swallowing mechanism affecting bolus propulsion from the oral cavity to the level of the pharyngoesophageal junction, the level of the cricopharyngeal muscle, the upper esophageal sphincter (UES), or the cervical esophagus. Pharyngonasal regurgitation results from the retropulsion of the bolus into the nasal cavity, and laryngeal aspiration is a result of hypopharyngeal stasis and vallecula pooling. Both are a consequence of a functional or structural obstruction, impeding bolus propulsion.

Dysphagia due to neurologic injury results from an injury to the central or peripheral nervous system, regardless of etiology. Bilateral cortical damage such as that following a cerebrovascular accident can result in reduced lingual control and loss of initiation of the swallowing reflex, which results in delayed swallowing and reduced pharyngeal peristalsis. Infarcts affecting the control centers for the nucleus ambiguus cause unilateral paralysis of the pharyngeal and laryngeal musculature, resulting in poor glottic closure complicated by hypopharyngeal stasis and laryngotracheal aspiration. Amyotrophic lateral sclerosis is a progressive neurodegenerative disease causing motor neuron degeneration in the brain, brainstem, and spinal cord. Weakness, muscle atrophy, and fasciculation of the musculature lead to poor bolus handling, resulting in abnormal swallowing. Delayed or incomplete opening of the UES leads to hypopharyngeal stasis, vallecular pooling, and, ultimately, laryngotracheal aspiration. Lesions to the cranial nerves innervating the UES can cause uncoordinated or reduced sphincter opening, leading to a functional obstruction of the UES; this obstruction coupled with a contracting pharynx may cause pharyngooral regurgitation, resulting in pharyngolaryngotracheal aspiration or nasal regurgitation. Neurogenic swallowing abnormalities are visualized by videofluoroscopy. The traditional method uses a single form of liquid barium swallow and is performed by a radiologist. The currently preferable, modified method uses multiple barium-infused consistencies for swallowing and is performed by a speech pathologist. The modified barium study has the oral pharyngeal advantage of being able to capture subtle abnormalities in bolus transfer from the oral cavity to the pharyngoesophageal border. Treatment of disordered swallowing secondary to cortical disturbances begins with education, dietary manipulation, and relearning techniques; alternative nutrition routes, such as a percutaneously placed feeding tube, are reserved for advanced disease. Cricopharyngeal myotomy has been tried with some degree of success in the treatment of cricopharyngeal dysfunction induced by cranial nerve damage. The goal of this procedure is to provide a less obstructed route for the bolus to travel through for entrance into the esophagus (see Plate 2-72).

Dysphagia secondary to a primary muscle disease is best illustrated with a progressive degenerative disease such as muscular dystrophy, particularly the oculopharyngomuscular variant. Bilateral ptosis is a primary manifestation of the disease, with dysphagia appearing prior to or simultaneously with the ptosis. They are both late and progressive manifestations of the disease. Pharyngooral regurgitation is characteristic of dysphagia resulting from a weak pharyngeal musculature incapable of peristaltic contractions of sufficient amplitude

KILLIAN TRIANGLE, ENDOSCOPIC ELECTROCAUTERY, CRICOPHARYNGEAL BAR



Videofluoroscopic image demonstrating classic cricopharyngeal "bar" (arrow)—posterior indentation of cricopharyngeus muscle with concomitant narrowing of esophageal lumen (From Damrose EJ, Ho AS. *Operative Techniques in Otolaryngology-Head and Neck Surgery*. Elsevier, Philadelphia, 2012.)

to move the bolus through the UES. Tracheobronchial symptoms occur from poor control of laryngeal muscles, pharyngeal muscle weakness, and hypopharyngeal stasis. Videofluoroscopy demonstrates normal initiation of swallowing, impaired barium clearance from the pharynx with concurrent vallecular pooling, and reduced UES opening due to incomplete or delayed relaxation, with many demonstrating a cricopharyngeal bar. Treatment is traditionally supportive and includes dietary manipulation, education, and counseling, plus alternative nutritional feeding when the disorder is severe. Cricopharyngeal myotomy has been used with good results in small patient series. The success of the procedure likely results from enlargement of the

pharyngoesophageal opening following the myotomy. Simply stated, a path of least resistance is created by the procedure.

Cricopharyngeal achalasia presents with oropharyngeal dysphagia due to cricopharyngeal dysfunction that may or may not coexist with a pharyngeal diverticulum (Zenker diverticulum). Cricopharyngeal achalasia is characterized by incomplete relaxation of the UES or by a lack of coordination between UES opening and pharyngeal contractions. It can arise from an intrinsic muscle defect or from underlying neurologic dysfunction producing high UES pressures. By definition, there should be strong pharyngeal contractions acting against a poorly relaxing UES, a condition that presents

CRICOPHARYNGEAL MYOTOMY AND ESOPHAGEAL DIVERTICULA

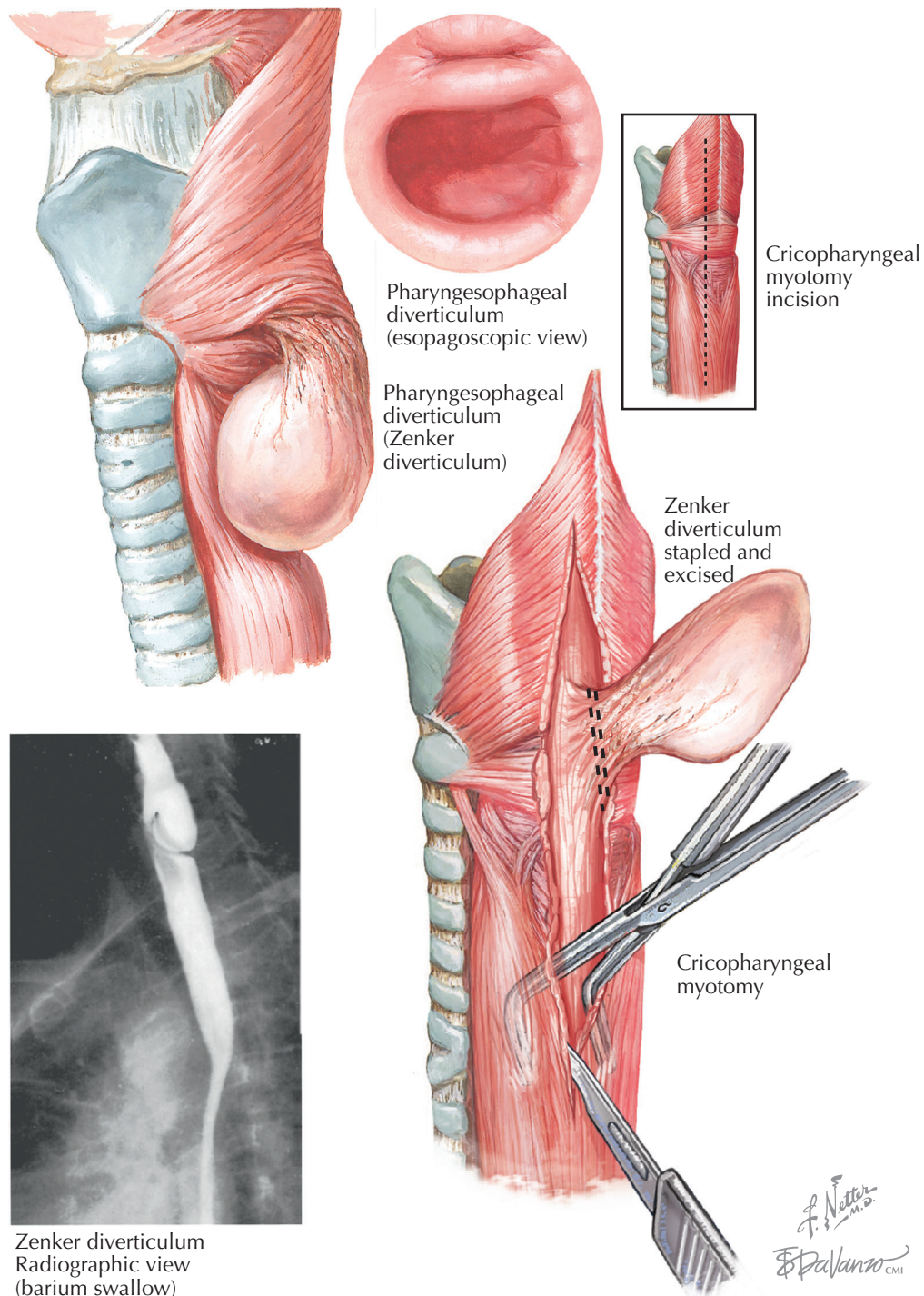
FUNCTIONAL DISORDERS THAT LEAD TO STRUCTURAL ISSUES

(Continued)

as a functional obstruction. Patients with cricopharyngeal achalasia present with symptoms of dysphagia primarily for solids, pharyngooral regurgitation resulting from the strong pharyngeal contractions acting against a noncompliant UES, and resultant laryngotracheal aspiration. Videofluoroscopy demonstrates barium pooling above a closed UES with or without the presence of a cricopharyngeal bar. A restrictive myopathy secondary to fibrosis or an infiltrative process causing the reduced compliance of the cricopharyngeus muscle has been implicated in the pathogenesis; however, because the response to successive bougie pharyngo-esophageal dilations is inconsistent, disease at the level of the muscle is not likely to be the only causative factor in this condition. Manometric findings of a hypertensive UES and a frequent positive response to botulinum toxin suggest an imbalance in excitatory inhibition from acetylcholine receptors and inhibitory neurotransmitters, as seen in classic achalasia. Botulinum toxin has been shown to be an effective temporary therapy reducing cricopharyngeal achalasia in adults and children in much the same way as it has been used in esophageal achalasia. In this condition commercially manufactured botulinum toxin is diluted with preservative-free normal saline, and under endoscopic visualization, an injection of the medication is placed in each of the four quadrants of the UES. Botulinum toxin irreversibly destroys the treated acetylcholine receptor; however, this treatment is temporary, lasting only 6 to 9 months, due to growth of new receptors. The correlation of symptoms with radiologic dysfunction, manometric abnormalities of a hypertensive UES, and poor pharyngeal clearance favors a positive response to botulinum injections and a good response to cricopharyngeal myotomy by either surgical or endoscopic techniques.

Cricopharyngeal bar is a radiographic finding that presents as a prominent and persistent posterior indentation at the level of the lower third of the cricoid cartilage; it is best seen on lateral views. Histologically, degenerative muscle fibers and fibrosis were found on dissected surgical specimens. They are present in both symptomatic and asymptomatic individuals. Esophageal dilation has been successfully used to treat dysphagia in elderly individuals with a cricopharyngeal bar.

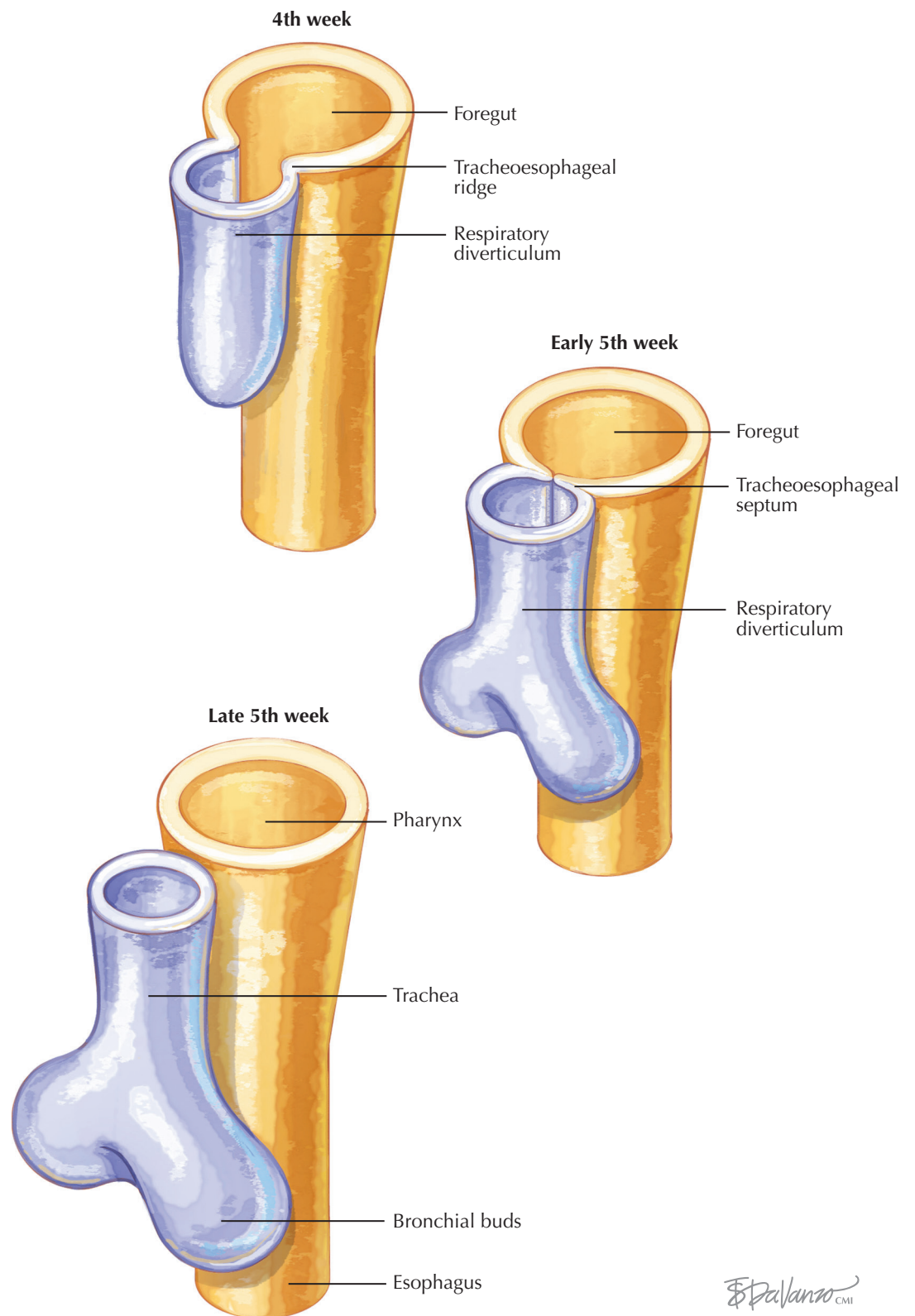
Zenker diverticulum is formed in an area of anatomic weakness known as the Killian triangle, which is bordered inferiorly and posteriorly by the superior fibers of the cricopharyngeal muscle and superiorly by the inferior fibers of the inferior constrictor muscles of the posterior pharynx. This diverticulum, or outpouching, is created by strong pharyngeal peristaltic contractions against a noncompliant upper esophageal or cricopharyngeal sphincter. This poorly coordinated movement creates high intrabolus pressures within the hypopharynx, leading to the development of a pulsion diverticulum. Symptoms and complications of the diverticulum vary with the size of the lesion. The most common presenting symptoms include dysphagia, regurgitation of undigested food, especially in the supine position, choking, aspiration, and halitosis. A small diverticulum is typically asymptomatic and incidentally found on upper endoscopy or during a barium examination. On radiologic evaluation, the pharyngo-esophageal diverticulum is seen as a midline protrusion



at the level of the posterior hypopharyngeal wall, just above the cricopharyngeal muscle. A large diverticulum can cause considerable anatomic distortion, leading to a functionally obliterated or closed esophageal lumen. Because progressive enlargement is rare, in individuals with a small diverticulum, observation may be the only required intervention; in patients with large symptomatic diverticula, surgical or endoscopic management is required. Because the diverticulum developed as a result of a noncompliant cricopharyngeal muscle, therapeutic intervention involves two steps, diverticulectomy and cricopharyngeal myotomy. Traditionally, treatment was surgical with an open or a transoral endoscopic approach using a rigid or flexible endoscope. Regardless of the mode of entrance, large diver-

ticula can be inverted, suspended (diverticulopexy), or resected. Today the endoscopic approach is favored for diverticula of less than 5 cm. A single lumen is created with ablation of the upper esophageal sphincter by incising the muscular layer of the septum, which is composed of the posterior esophageal wall and anterior wall of the diverticulum and includes the upper esophageal sphincter. Recurrence is rare when a cricopharyngeal myotomy is performed at the same time as the diverticulectomy. Flexible endoscopic techniques have been shown to be as safe as rigid endoscopic treatment for diverticula that are less than 5 cm, and they have the advantage of not requiring general anesthesia. Myotomy can be done using the needle knife technique, argon plasma coagulation, and a monopolar forceps.

ESOPHAGUS



DEVELOPMENT OF ESOPHAGUS

The esophagus is the first section of the foregut and begins at the distal end of the pharynx. As with the rest of the digestive tract, the cells that line the lumen of the esophagus are derived from endoderm. The supporting structures of the esophagus come from two different sources, although they are all innervated by the vagus nerve. The muscles and connective tissues of the esophagus's proximal third are derived from the mesenchyme of the pharyngeal arches. Like the pharynx, the skeletal muscle of the superior esophagus is innervated by axons from the nucleus ambiguus traveling in the vagus nerve. The muscles and connective tissues of the distal third of the esophagus are derived from the visceral mesoderm that surrounds the gut tube. For this reason, the muscular layers of this area are composed of smooth muscle, innervated largely by the dorsal vagal motor nucleus, also traveling in the vagus nerve. The middle third of the esophagus blends the characteristics of the other two, containing both skeletal and smooth muscle.

The development of the esophagus is intimately related to that of the trachea. At the distal end of the pharynx during the fourth week, the *laryngotracheal groove* forms, leading to a short blind pouch, the *respiratory diverticulum*. The respiratory diverticulum is a pouch of endoderm that extends ventrally into the nearby visceral mesoderm. By the fifth week the respiratory diverticulum has elongated into a *tracheal bud* that stretches inferiorly and is completely separate from the esophagus except for its connection at the primordial *laryngeal inlet*, which will eventually become the *glottis*. The separation of the two tubes is effected by

two ridges of visceral mesoderm, the *tracheoesophageal ridges*. These ridges grow medially between the respiratory diverticulum/tracheal bud and the esophagus, eventually forming a *tracheoesophageal septum*. This process occasionally goes awry, resulting in congenital anomalies such as blind pouches and tracheoesophageal fistulas.

The esophagus is initially relatively short but elongates to its normal relative length by the seventh week. If it fails to lengthen appropriately, it can produce a

congenital hiatal hernia from the traction placed on the developing stomach as it passes through the diaphragm. The proliferation of the endodermal cells of the esophageal lumen is one of the factors that allow it to lengthen. The lumen typically becomes obstructed by these epithelial cells but recanalization opens the lumen during the eighth week. Failure of the lumen to recanalize may lead to an abnormal narrowing, esophageal stenosis, as well as polyhydramnios, because the fetus is unable to swallow amniotic fluid.

Ed Ballman CMI

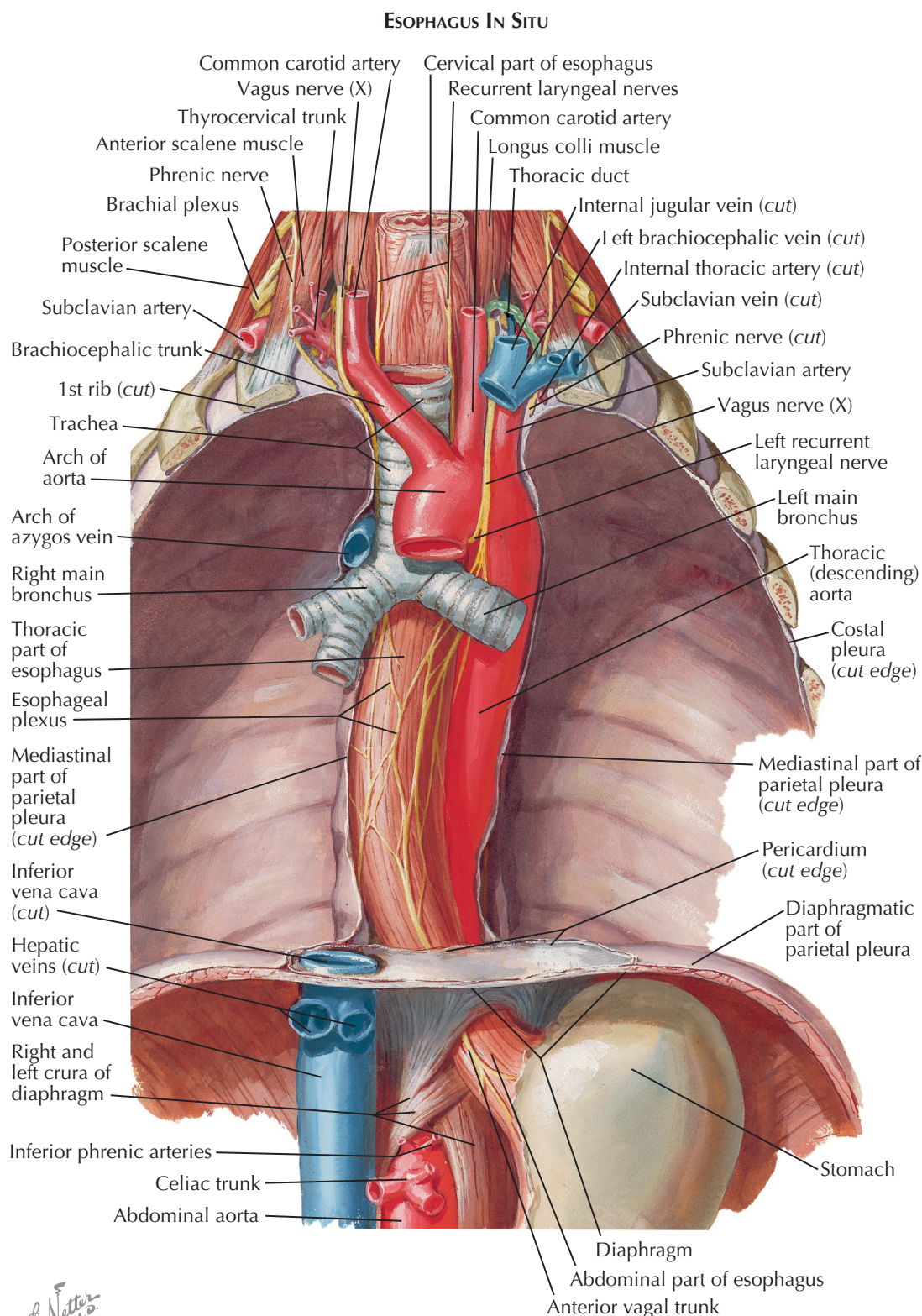
TOPOGRAPHIC RELATIONSHIPS; CONTOURS AND NORMAL CONSTRICTIONS OF ESOPHAGUS

The esophagus begins in the neck as a continuation of the pharynx (*cervical esophagus*). This point of origin corresponds to the inferior border of the *cricoid cartilage* and the lower margin of the *inferior pharyngeal constrictor muscle*, also called the *cricopharyngeus muscle*, at about the level of the sixth cervical vertebra. The esophagus extends inferiorly through the neck and through the superior and posterior mediastina of the thorax. It then passes through the esophageal hiatus of the *diaphragm* to join the cardiac region of the stomach at about the level of the 10th thoracic vertebra.

The esophagus generally follows the anteroposterior curvature of the vertebral column, except in the inferior portion, which is tethered by its relationship with the diaphragm. It also forms two lateral curvatures, so that in a coronal view, it assumes the form of a gentle reversed "S." The upper of the two lateral curvatures is convex toward the left, and the lower curvature, in the lower thorax and abdomen, is convex toward the right. From its commencement at the lower margin of the cricoid cartilage, the esophagus inclines slightly to the left until its left border projects approximately one-fourth inch to the left of the tracheal margin. It then swings somewhat to the right, reaching the midline at about the level of the fourth thoracic vertebra behind the aortic arch. It continues its inclination to the right until about the level of the seventh thoracic vertebra, where it again turns left somewhat more sharply than in its previous curves, and in this direction it passes through the esophageal hiatus.

The esophagus has cervical, thoracic, and abdominal portions. Anterior to the cervical portion lies the membranous posterior wall of the trachea, to which it is rather loosely connected by loose connective tissue and some smooth muscular strands, so that the anterior esophageal and the posterior tracheal walls are occasionally referred to as the "common party wall." In the grooves on each side between the trachea and the esophagus are the *recurrent laryngeal nerves*, which ascend from the vagus nerves in the upper thorax to reach the larynx. Posteriorly, the esophagus lies upon the prevertebral fascia, covering the anterior surface of the *longus colli muscles* and cervical vertebral bodies. On the left and right, the *carotid sheath* and the structures it contains (vagus nerve, carotid arteries, and internal jugular vein) accompany the cervical esophagus. Owing to the curvature of the esophagus in this region, it lies closest to the left carotid sheath. The lobes of the *thyroid gland* partially overlap the esophagus on each side. The *thoracic duct* ascends in the root of the neck on the left side of the esophagus and then arches laterally posterior to the carotid sheath and anterior to the *vertebral artery and vein* to enter the left *brachiocephalic* or left *subclavian vein* at the medial margin of the *anterior scalene muscle*.

The *thoracic esophagus* also lies posterior to the trachea as far as the level of the fifth thoracic vertebral body, at which point the trachea bifurcates. The trachea deviates slightly to the right at its lower end, so that the *left main*



bronchus crosses anterior to the esophagus. Below this point the esophagus is separated anteriorly from the left atrium of the heart by the pericardium. In the very lowest portion of its thoracic course, the esophagus passes posterior to the central tendon of the diaphragm to reach the esophageal hiatus. On the left side in the superior thoracic region, the esophageal wall contacts the ascending portion of the left subclavian artery and the *parietal pleura*; at about the level of the fourth thoracic vertebra, the *arch of the aorta* passes posteriorly

alongside the esophagus. Below this point the *descending aorta* lies to the left, but when it passes posterior to the esophagus, the left mediastinal pleura again comes to abut on the esophageal wall. On the right side the right *parietal pleura* is intimately applied to the esophagus, except when, at about the level of the fourth thoracic vertebra, the azygos vein intervenes as it turns anteriorly. The short *abdominal portion* of the esophagus lies upon the diaphragm and makes an impression on the liver with its anterior aspect.

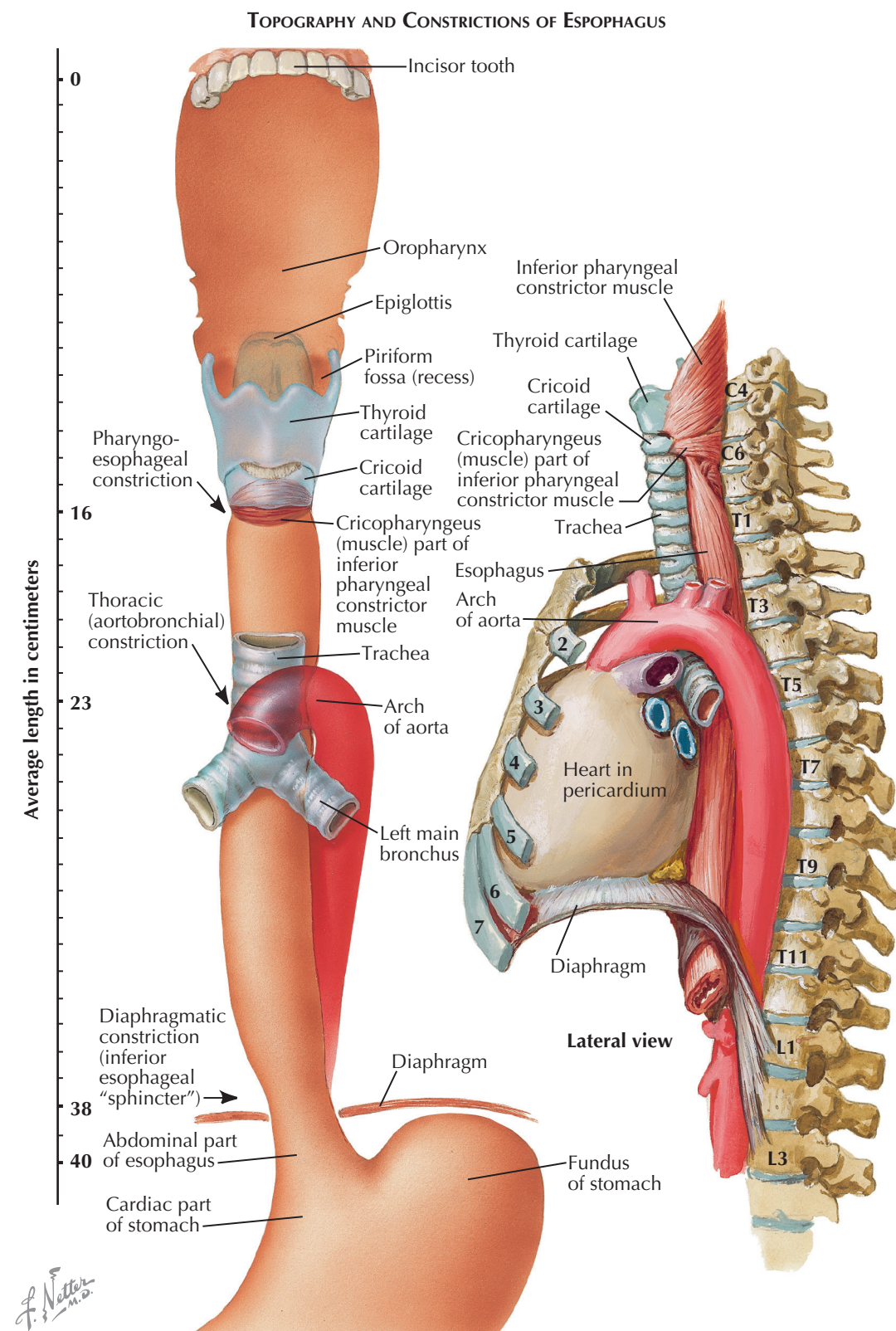
TOPOGRAPHIC RELATIONSHIPS; CONTOURS AND NORMAL CONSTRICTIONS OF ESOPHAGUS (Continued)

The left and right vagus nerves associate with the esophagus, and below the tracheal bifurcation, they interweave to form the *esophageal plexus* of nerves. This plexus then coalesces with the *anterior* and *posterior vagal trunks* that pierce the diaphragm along the esophagus.

The course of the esophagus is marked by several indentations and constrictions:

1. The first narrowing of the esophagus is found at its commencement, caused by the cricopharyngeus muscle at the inferior border of the inferior pharyngeal constrictor and the cricoid cartilage.
2. The esophagus is indented on its left side by the arch of the aorta (*aortic constriction*), and at this level the aortic pulsations may often be observed through the esophagoscope.
3. Just inferior to this point the left main bronchus causes an impression on the left anterior aspect of the esophagus.
4. At its lower end the esophagus is narrowed by the *diaphragmatic constriction* (*inferior esophageal sphincter*) as it passes through the *right diaphragmatic crus*.

The overall length of the esophagus varies in accordance with the length of the trunk of the individual. The average distance of the cardia from the upper incisor teeth is approximately 40 cm, but in some "long" individuals this distance may be as much as 42 or 43 cm. This average distance of 40 cm may be subdivided as follows: The distance from the incisor teeth to the cricopharyngeus muscle, which corresponds to the commencement of the esophagus, averages 16 cm. It is thus apparent that the average length of the esophagus itself is 40 minus 16 cm equals 24 cm, or approximately 10 inches. At about 23 cm from the incisor teeth, the arch of the aorta crosses the esophagus on its left side. This crossing is therefore about 7 cm below the cricopharyngeus. A few centimeters below this point the left main bronchus passes anterior to the esophagus. The diaphragmatic constriction, or com-



mencement of the abdominal part of the esophagus, is located at about 37 to 38 cm from the incisor teeth. It is of considerable significance to note that the esophageal hiatus of the diaphragm is slightly inferior (≈ 1 cm) to this point, and the cardiac region of the stomach is at a still slightly lower level. The figures given above are for adults; in children the dimensions are proportionately smaller. At birth the distance from the incisor teeth to the cardiac region is usually only 18 cm, at 3

years approximately 22 cm, and at 10 years approximately 27 cm.

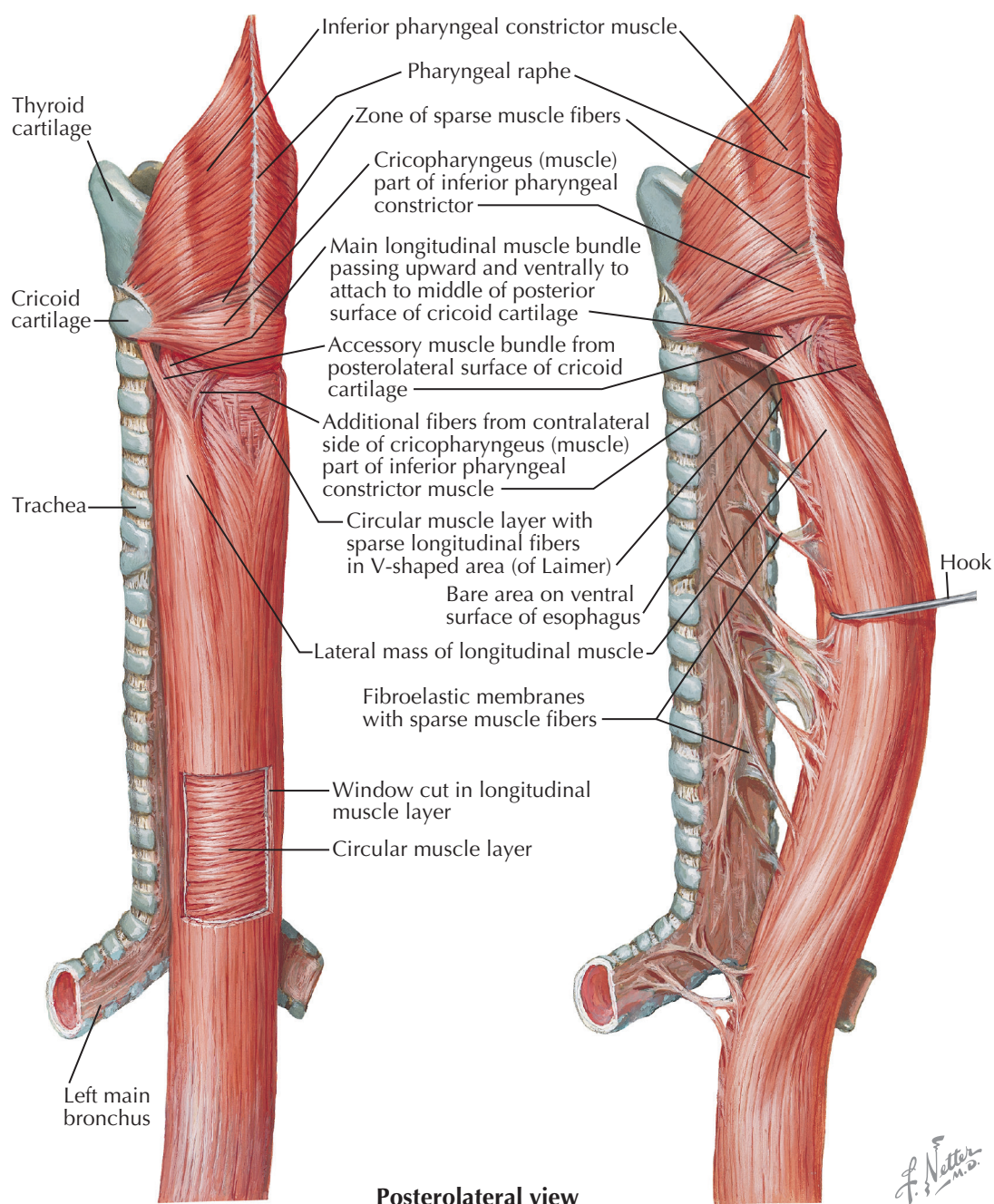
Although the esophagus is usually described as tube-like, it is generally flattened so that the transverse axis is somewhat larger than the anteroposterior axis. In the resting state the esophageal walls are in approximation. The width or diameter of the esophagus varies considerably with its state of tonus, but the average resting width is approximately 2 cm.

MUSCULATURE OF ESOPHAGUS

MUSCULATURE OF ESOPHAGUS

The musculature of the esophagus consists of an outer *longitudinal muscle* layer and an inner muscular layer, generally described for convenience as the *circular muscle layer*; although, strictly speaking, the term “circular” is not properly accurate, as will be seen below. The outer longitudinal muscle layer originates principally from a stout tendinous band that is attached to the upper part of the vertical ridge on the dorsal aspect of the cricoid cartilage. From this tendon two muscle bands originate and diverge as they descend and sweep around the right and left sides of the esophagus. They meet and interdigitate somewhat in the posterior midline, leaving a V-shaped gap superior to and between them. This gap is known as the *V-shaped area* (of Laimer), and the base of the area is formed by the underlying circular muscle. Superiorly, it is bounded by the cricopharyngeus muscle. A few sparse fibers of the longitudinal muscle spread over this area, as do some accessory fibers from the lower margin of the cricopharyngeus. The longitudinal muscle fibers are not uniformly distributed as they descend over the surface of the upper esophagus. Instead, the fibers gather into thick *lateral longitudinal muscle masses* on each side of the esophagus, but they remain considerably thinner over other parts of the tube. The muscle is thinnest on the anterior wall (i.e., the wall that is applied to the posterior surface of the trachea). Indeed, high up on the esophagus's anterior surface, the longitudinal muscle is said to be entirely lacking, and this portion of the esophagus is designated as the “*bare*” area. The longitudinal muscle of the esophagus also usually receives additional contributions by way of *accessory muscle* slips on each side, which originate from the posterolateral aspect of the cricoid cartilage and also from the contralateral side of the deep portion of the cricopharyngeus muscle. As the longitudinal muscle descends, it progressively forms a more uniform sheath over the entire circumference of the esophagus. The anterior wall of the esophagus is firmly applied to the posterior tendinous wall of the trachea in its upper portion where the two organs are attached to each other by *fibroelastic membranous tissue* containing some muscle fibers.

The inner, so-called *circular layer* of esophageal muscle underlies the longitudinal muscle layer.



Although a definite layer, it is slightly thinner than the longitudinal coat. This ratio of longitudinal and circular muscle coat is unique for the esophagus and is reversed in all other parts of the alimentary tract. The circular layer in the upper esophagus is not truly circular but rather elliptical, with the anterior part of the ellipse at a lower level than the posterior part. The inclination of the ellipses becomes less as the esophagus descends, until, at about the junction of the upper and middle

thirds, the fibers run in a truly horizontal plane. Here, for a segment of about 1 cm, they may be said to be truly circular. Below this point they again become elliptical, but the inclination is reversed from that of the higher fibers (i.e., the posterior part of the ellipse now assumes a lower level than the anterior part). In the lower third of the esophagus, the course of the fibers again changes to a screw-shaped or spiral course, winding progressively inferiorly as they pass around the

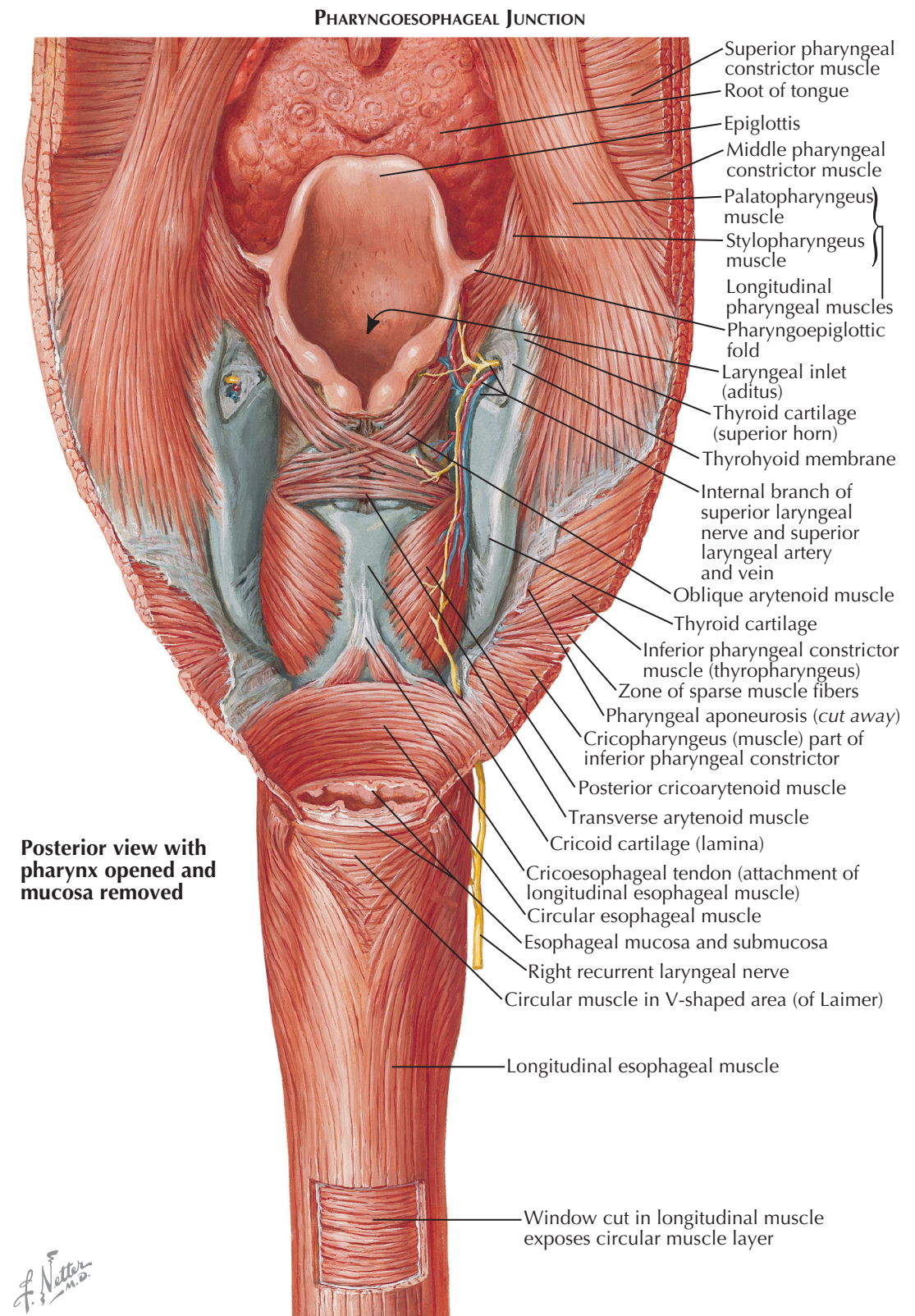
MUSCULATURE OF ESOPHAGUS (Continued)

esophagus. It should be noted also that the elliptical, circular, and spiral fibers of this layer are not truly uniform and parallel but may overlap and cross or even have clefts between them. Some fibers in the lower two thirds of the esophagus occasionally leave the elliptical or spiral fibers at one level, to pass diagonally or even perpendicularly upward and downward to join the fibers at another level, but they never form a continuous layer. They may be threadlike or 2 to 3 mm in width and from 1 to 5 cm in length; they are usually branched. The musculature of the esophagogastric junction will be discussed in the next section. Spontaneous rupture of the esophagus almost invariably occurs in the lower 2 cm of the esophagus. A linear tear may occur through the entire thickness of the esophageal wall. Severe vomiting predisposes to rupture of this region, releasing gastric juice into the mediastinum.

The *cricopharyngeus muscle*, although strictly speaking a muscle of the pharyngeal wall, being the lowermost portion of the *inferior constrictor of the pharynx*, is nevertheless of great importance in the function and malfunction of the esophagus. This narrow band of muscle fibers originates on each side from the posterolateral margin of the cricoid cartilage and passes slinglike around the posterior aspect of the pharyngoesophageal junction. Its superiormost fibers ascend to join the median raphe of the inferior constrictor muscle posteriorly. The cricopharyngeus also has muscle fibers that run horizontally to encircle the pharyngoesophageal junction, acting as the superior pharyngeal constrictor. This cricopharyngeal constriction is felt when an esophagoscope is introduced, because even at rest the muscular tonus felt within the esophageal lumen is greater at the level of the cricopharyngeus than in other parts of the esophagus, and the relaxation of this muscle

Posterior view with
pharynx opened and
mucosa removed

F. Netter M.D.



is an integral part of the act of swallowing. Superior to the cricopharyngeus (between this muscle and the main part of the inferior constrictor) the musculature is somewhat weaker and sparser posteriorly. It is through this sparse area that most Zenker diverticula are believed to originate.

The musculature of the upper portion of the esophagus is striated, whereas that of the lower portion is made up almost entirely of smooth muscle. The level at which

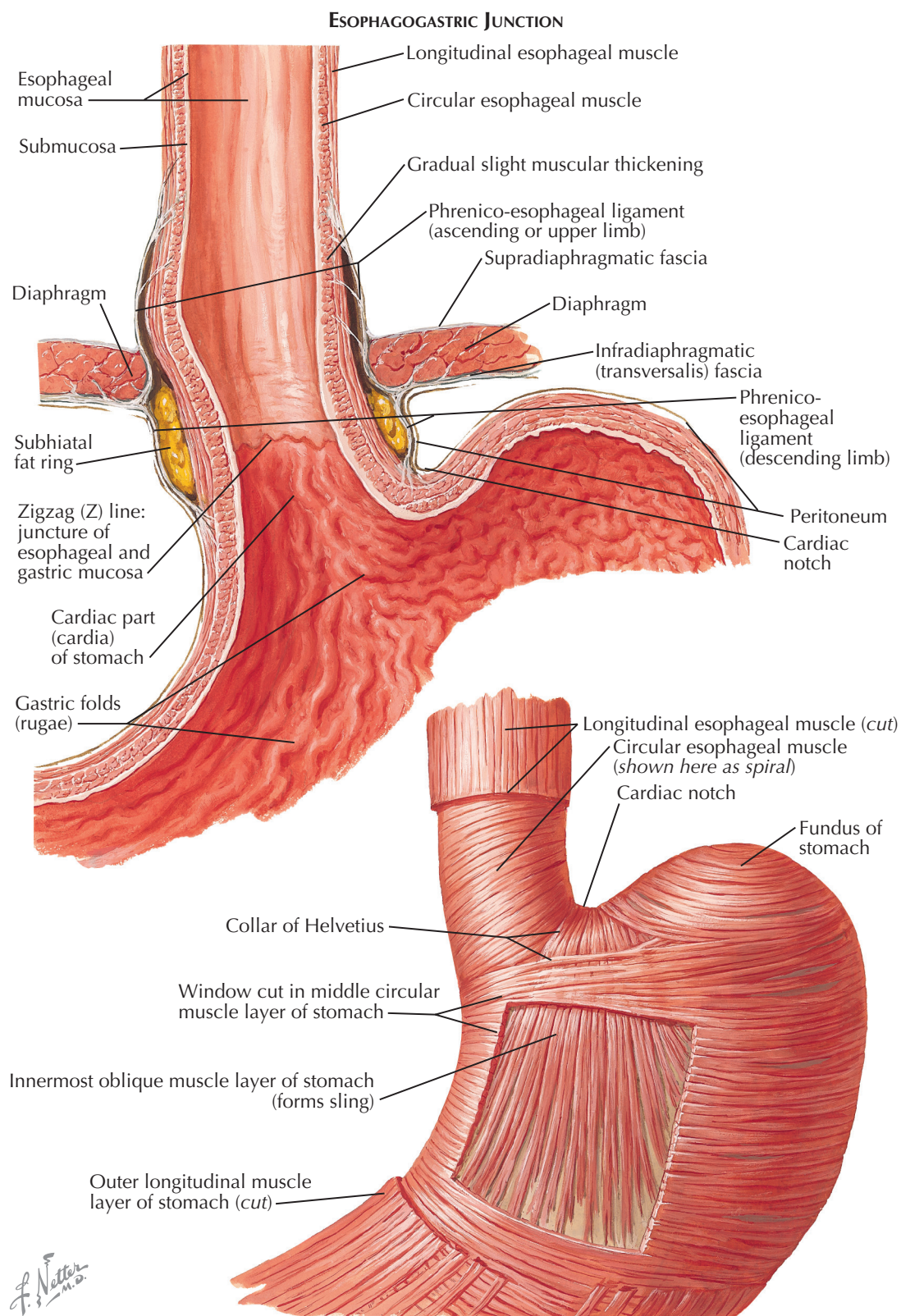
this transition takes place varies. In general, it may be said that the upper fourth of the esophagus contains purely striated muscle, the second fourth is a transitional zone in which both striated and smooth muscle are present, and the lower half contains purely smooth muscle. Between the longitudinal and circular coats of the esophageal muscles is a narrow layer of connective tissue where the myenteric ganglia and plexus (of Auerbach) can be found.

ESOPHAGOGASTRIC JUNCTION

The structure and function of the distal esophagus and its junction with the stomach have been the subject of much investigation. This has led to an improved understanding of clinical ailments such as achalasia, hiatal hernia, Barrett esophagus, esophagitis, and peptic ulcer of the esophagus. The longitudinal muscle coat of the esophagus extends inferiorly and continues over the surface of the stomach as the outer *longitudinal layer* of the smooth muscle of the stomach. The so-called inner circular layer of esophageal musculature, which at this point is spiral in character, also continues over the stomach but divides, in the region of the cardia, into the middle *circular layer* of the gastric musculature and the inner *oblique layer* of muscle fibers. The esophagus's inner oblique muscle fibers pass slinglike across the *cardiac notch*, whereas the middle circular fibers pass more or less horizontally around the stomach. These two layers of muscle fibers thus cross each other at an angle, forming a muscular ring, which became known as the *collar of Helvetius*. To the left of the esophagus the oblique fibers form *sling fibers* that project from the anterior wall of the stomach to the posterior wall, making a tight bend around the cardiac notch. On the opposite side of the cardiac region, the circular layer has substantial *clasp fibers* that pinch and narrow the cardiac region. Acting together, the sling and clasp fibers help prevent gastric reflux and form a functional, but not anatomic, lower esophageal sphincter.

A gradual but moderate thickening of both the so-called *circular and longitudinal muscles* takes place in the lower end of the esophagus, commencing about 1 or 2 cm above the *esophageal hiatus* through the diaphragm and extending to the cardia. This region of thickened musculature has been termed the "esophago-gastric vestibule" and this region contracts and relaxes as a unit. It is believed that the bolus is transiently arrested just above the esophageal hiatus by the tonicity of the distal esophagus and, contrariwise, that its passage into the stomach is made possible by the relaxation of the muscles working as an integrated or coordinated unit. It is likewise believed that the contraction of the distal esophagus is one of the important factors in the prevention of regurgitation from the stomach. Other factors in the prevention of regurgitation are believed to be the angulation of the esophagus as it passes through the diaphragm while passing over into the stomach and a rosette-like formation of loose gastric mucosa at the cardia. The possibility of sphincteric action of the diaphragm is debated, although it is recognized that in deep inspiration, when the diaphragm is in strong contraction, passage into the stomach may be impeded.

The mucosa of the esophagus is smooth and rather pale in color. When the esophagus is contracted, the mucosa is gathered up into irregular longitudinal folds. The gastric mucosa, on the other hand, is a much deeper red in color, with well-defined folds, rugae, in the lumen of the organ. The transition from esophageal



to gastric mucosa occurs rather sharply and is easily recognizable by a change in epithelial color. This transition takes place along an irregular dentate or zigzag line, sometimes called the *Z line*. The Z line marks the transition from stratified squamous of the esophagus to simple columnar epithelium of the stomach; it usually does not coincide with the anatomic border of the cardia but is slightly superior to it, between the level of the cardia and the esophageal hiatus. In some instances

the gastric mucosa may extend for a considerable distance into the esophagus.

In its passage through the esophageal hiatus of the diaphragm, the esophagus is surrounded by the *phrenicoesophageal ligament*, also known as the phrenoesophageal ligament or diaphragmaticoesophageal ligament. The phrenicoesophageal ligament arises from the circumference of the esophageal hiatus as an extension of the *infradiaphragmatic fascia*, which is continuous with

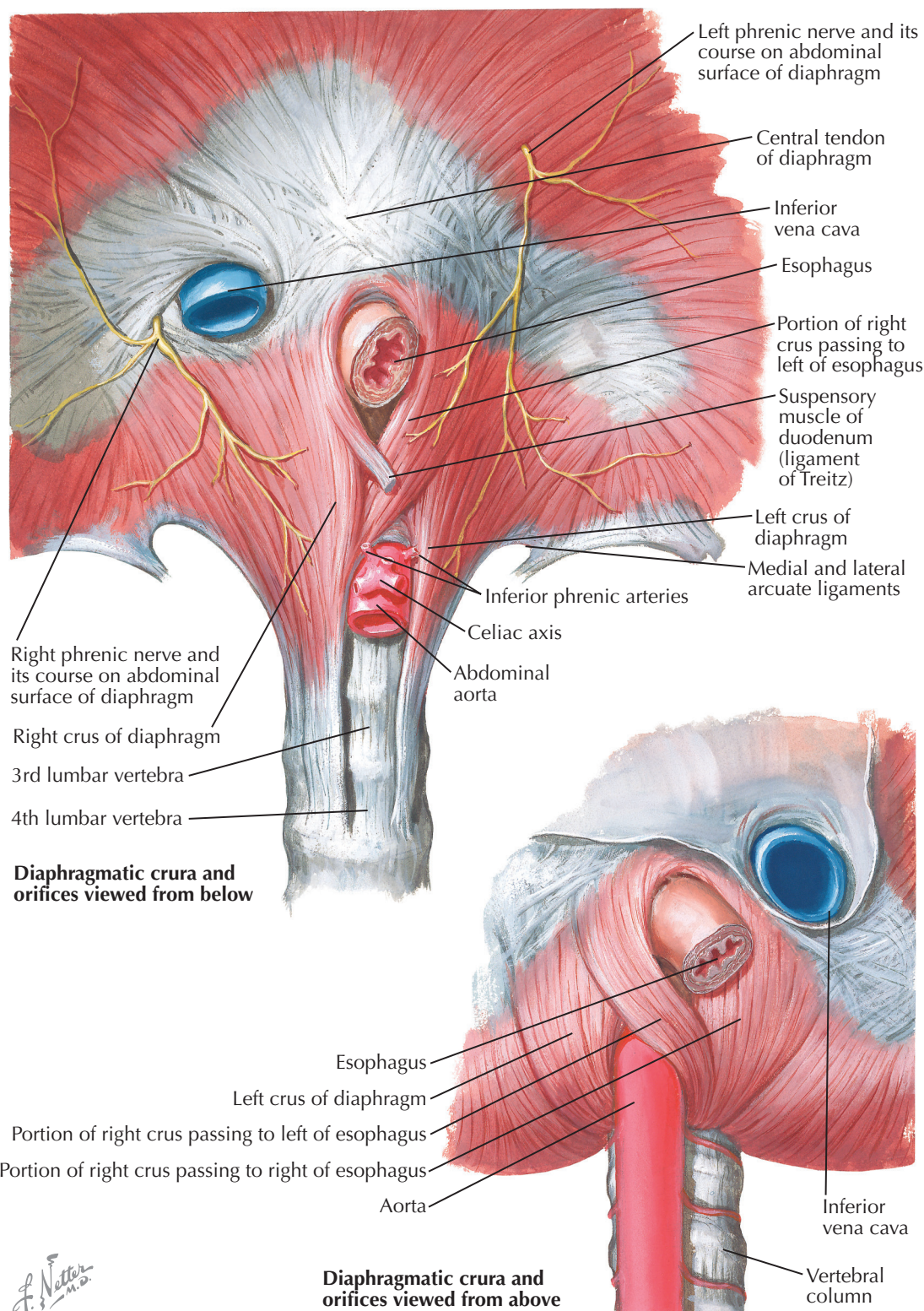
ESOPHAGOGASTRIC JUNCTION

(Continued)

the *transversalis fascia*. At the margin of the hiatus, it divides into an *ascending limb* and a *descending limb*. The ascending limb passes superiorly through the esophageal hiatus and surrounds the esophagus in a tentlike fashion. It extends for several centimeters above the hiatus and inserts circumferentially into the adventitia of the esophagus. The descending limb passes inferiorly and inserts around the cardia deep to the *peritoneum*. The two limbs of the phrenicoesophageal ligament form a space superficial to the esophagus, in which lies a ring of rather dense fat. The function of the phrenicoesophageal ligament has been the subject of much speculation. From its structure it certainly would seem to play, fixing the distal esophagus in place while permitting the limited excursion required for respiration, deglutition, and postural changes. It also serves as an additional means of preventing pressure transmission through the esophageal hiatus. It may also in some manner take part in the closure or sphincteric mechanism of the esophagus in connection with diaphragmatic action.

The configuration of the esophageal hiatus of the diaphragm is interesting in that the distal esophagus is directed toward the left yet the hiatus is formed almost entirely by the *right crus of the diaphragm*; the *left crus of the diaphragm* plays no part in the formation of the esophageal hiatus. One band of muscle fibers, originating from the right crus, ascends and passes to the right of the esophagus. Another band of muscle fibers, originating also from the right crus but more deeply, ascends and passes to the left of the esophagus. These muscle bands overlap scissorwise and are inserted into the central tendon of the diaphragm. Thus, all the muscle fibers about the esophageal hiatus arise from the right crus of the diaphragm. It is interesting to note that those fibers of the right crus which pass to the right of the esophagus are innervated by the *right phrenic nerve*, whereas those which pass to the left of the esophageal hiatus appear to be innervated by a branch of the *left phrenic nerve*, as is also the left crus itself. The *right crus* of the diaphragm is usually considerably larger than is the left crus.

DIAPHRAGMATIC CRURA AND ORIFICES



Occasionally, one may find what has come to be known as the “muscle of Low.” This is a small band of muscle fibers that originates from the left crus and crosses over to the right, passing between the muscle fibers of the right crus to reach the central tendon in the region of the foramen of the *inferior vena cava*. Somewhat more frequently, a similar muscle bundle appears on the superior surface of the diaphragm. More significant is the fact that, in a considerable number of individuals, a variation may be found that has been

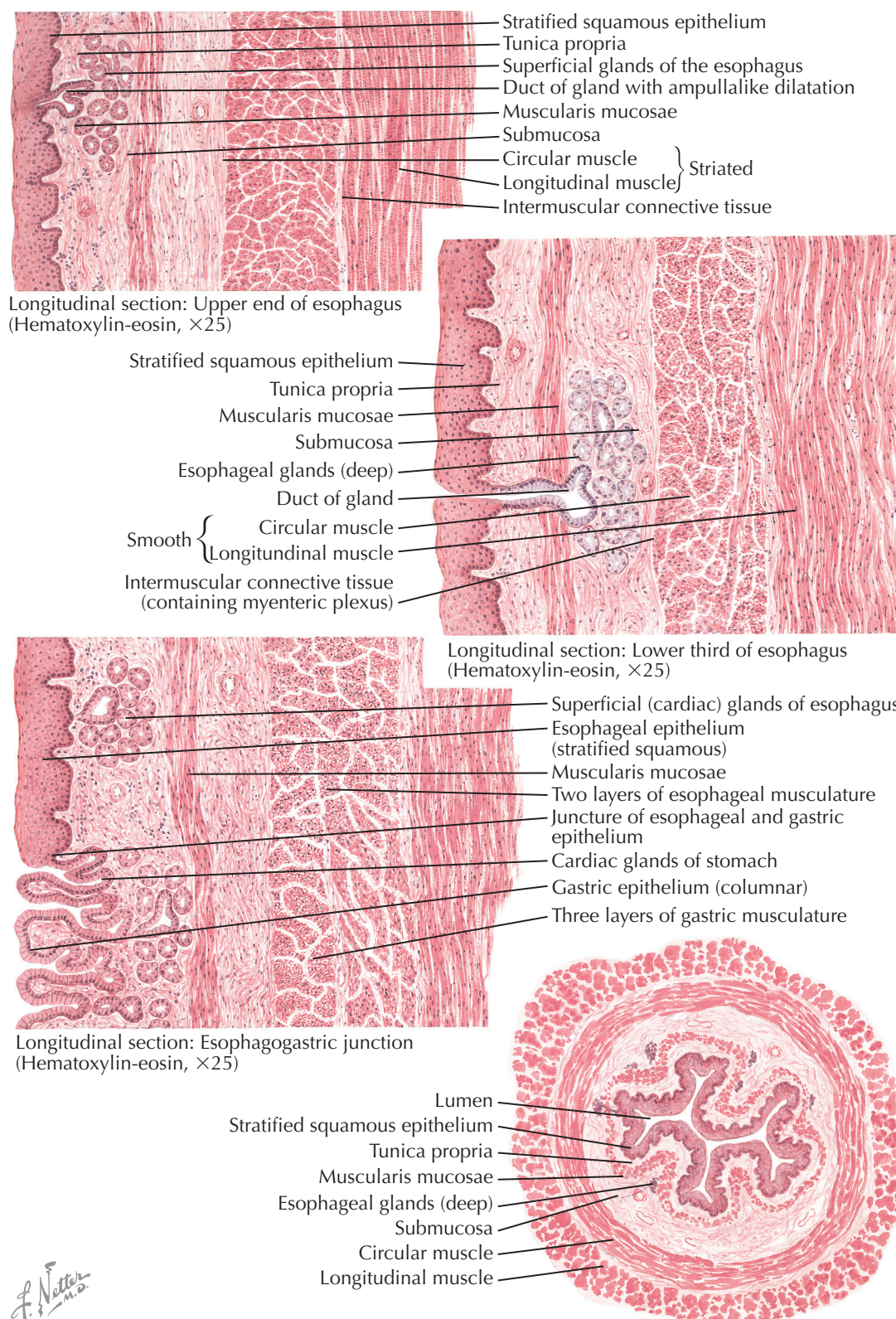
described as a “shift to the left.” In such cases fibers from the left crus of the diaphragm enter into formation of the right side of the esophageal hiatus. In some instances the muscles to the right of the esophageal hiatus may take origin entirely from the left crus and those to the left of the hiatus entirely from the right crus. The *suspensory muscle of the duodenum* (suspensory ligament of the duodenum, ligament of Treitz) typically originates from the fibers of the right crus of the diaphragm that pass to the right of the esophagus.

HISTOLOGY OF ESOPHAGUS

The esophagus, like other parts of the gastrointestinal tract, is made up of a *mucosa*, a *submucosa*, a *muscularis externa*, and an *adventitia*. The mucosa is subdivided into epithelium, lamina propria, and muscularis mucosae. The epithelium that lines the lumen of the esophagus is *stratified squamous epithelium*, which is continuous with the epithelial lining of the pharynx. The surface cells of this epithelium are flattened and contain a few keratohyaline granules, but do not form a keratinized layer. An abrupt transition takes place between the stratified squamous epithelium of the esophagus and the simple columnar epithelium of the stomach along an irregular zigzag line, known as the *Z line*, situated slightly superior to the cardiac region of the stomach. The *lamina propria* is a layer of loose connective tissue deep to the epithelium. The *muscularis mucosae* is a thin layer of smooth muscle deep to the lamina propria and is continuous with the pharyngeal aponeurosis. A transition from connective tissue to muscular tissue takes place in this aponeurosis at about the level of the cricoid cartilage. It contains both *longitudinal smooth muscle fibers* and some elastic tissue and is thicker at the lower end of the esophagus.

The *submucosa* is formed by dense irregular connective tissue and contains both elastic and type I collagen fibers, as well as blood vessels and nerves supplying the mucosa. Lymphocytes are scattered in moderate numbers through both the lamina propria and the submucosa, and occasionally these may be found in isolated concentric groups. In its contracted state, the esophageal mucosa is thrown into irregular longitudinal folds. The submucosa extends into these folds, but the more superficial muscular layers do not.

The *muscularis externa* consists of an inner *circular layer* and an outer *longitudinal layer*. A thin layer of connective tissue exists between the two layers, in which is embedded the *myenteric ganglia and plexus* (of Auerbach). Between the muscularis externa and the submucosa are the *submucosal ganglia and plexus* (of Meissner) and several blood vessels. The musculature of the upper one fourth of the esophagus is generally striated in character, the second fourth contains both striated and smooth muscle, and the lower half is composed entirely of smooth muscle. The *adventitia* is a layer of loose



connective tissue on the surface of the esophagus that anchors the organ to the surrounding structure.

Two types of glands can be recognized in the esophagus. The *esophageal glands proper* (of Brunner) are irregularly distributed throughout the entire length of the tube. They are small, compound mucous glands. Their ducts penetrate the muscularis mucosae and their branched tubules lie in the submucosa. They are somewhat more prominent in the superior part of the esophagus. The other type of glands is known as the *esophageal*

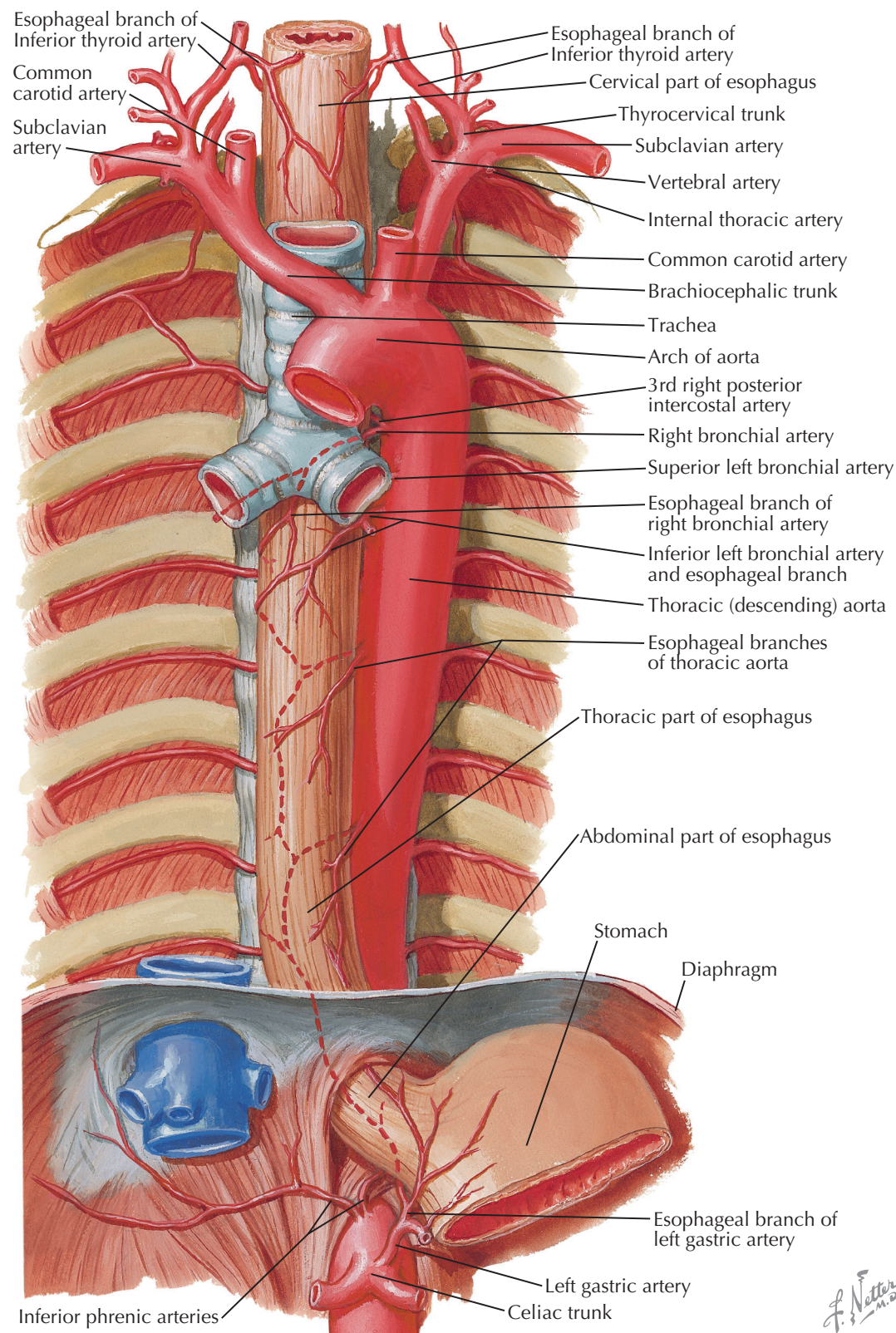
cardiac glands because they closely resemble or are identical with the cardiac glands of the stomach. They are found just above the cardiac region of the stomach, in the distal esophagus. They are also occasionally found proximally, a few centimeters below the level of the cricopharyngeus muscle. They differ from the esophageal glands proper in that their ducts do not penetrate the muscularis mucosae and their branched and coiled tubules are located in the lamina propria, *not* in the submucosa.

BLOOD SUPPLY OF ESOPHAGUS

The blood supply of the esophagus is extremely varied. The cervical region of the esophagus receives blood from *esophageal branches* of the *inferior thyroid artery*. The majority of esophageal branches arise from the terminal branches of this artery; its ascending and descending portions frequently give rise to one or more esophageal branches. The esophageal branches on the anterior aspect of the esophagus give small branches to the nearby trachea. Accessory arteries to the cervical esophagus may arise from the subclavian, common carotid, vertebral, ascending pharyngeal, superficial cervical, and thyrocervical arterial trunk.

The thoracic segment of the esophagus is supplied by branches from the (1) *bronchial arteries*, (2) *thoracic aorta*, and (3) *right intercostal arteries*. The bronchial arteries give off esophageal branches at or below the tracheal bifurcation, contributions from the *left inferior bronchial artery* being the most common. Patterns of the bronchial arteries vary markedly. The standard textbook type (two left, one right) occurs only in about one half of persons. Aberrant types are one right and one left (25%), two right and two left (15%), one left and two right (8%), and, in some instances, three right or three left. Near the bifurcation point of the trachea, the esophagus may receive additional twigs from the abdominal aorta, aortic arch, and intercostal and internal thoracic arteries. The aortic branches to the thoracic esophagus are not segmentally arranged, nor are they four in number, as commonly taught, but are only two unpaired vessels. The *superior esophageal branch of the thoracic aorta* is short (3 to 4 cm) and usually arises at the level of T6 to T7. The *inferior esophageal branch of the thoracic aorta* is longer (6 to 7 cm) and arises at the T7 to T8 disk level. Both arteries pass posterior to the esophagus and divide into ascending and descending branches that anastomose longitudinally, with descending branches from the inferior thyroid artery as well as bronchial arteries and with ascending branches from the left gastric and left inferior phrenic arteries. Right intercostal arteries, mainly the fifth, give rise to esophageal branches in about 20% of the population.

The abdominal esophagus receives its blood supply primarily through branches that arise from the celiac trunk. The left gastric artery is one of the three typical branches of this trunk and is the major blood supply to the abdominal esophagus. An additional blood supply comes from the *short gastric arteries* and from the *recurrent branch of the left inferior phrenic artery*, given off by the latter after it has passed posterior to the esophagus in its course to the diaphragm. The left gastric artery supplies cardioesophageal branches, either via a single vessel that subdivides or via several branches (two to five), given off in seriation before its division into an anterior and a posterior primary gastric branch. Other arterial sources to the abdominal esophagus may be branches from (1) an aberrant left hepatic from the left gastric, an accessory left gastric artery from the left



hepatic, or branches from a persistent primitive gastro-hepatic arterial arc; (2) cardioesophageal branches from the splenic trunk, its superior polar, terminal divisions (short gastric arteries), and its occasional large posterior gastric artery; or (3) a direct, slender cardioesophageal branch from the aorta or celiac or first part of the splenic artery.

With every resection operation, areas of devascularization may be induced by (1) a resection of the cervical

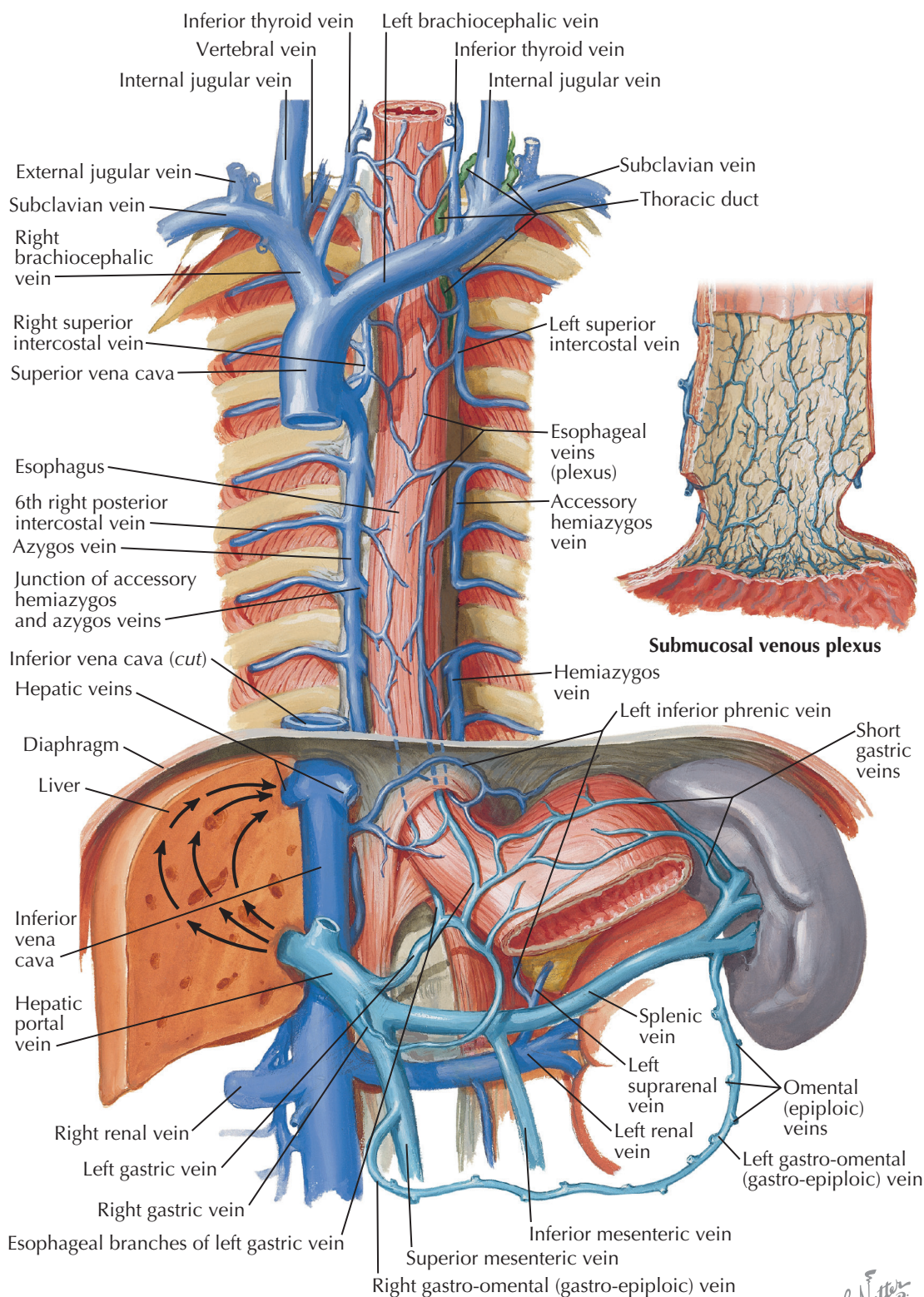
segment that is too low (the segment should always have a supply from the inferior thyroid); (2) excessive mobilization of the esophagus at the tracheal bifurcation and laceration of the bronchial arteries; or (3) excessive sacrifice of the left gastric and the recurrent branch of the left inferior phrenic to facilitate gastric mobilization. The anastomosis about the abdominal esophagus is usually very copious, but in some instances it may be extremely meager.

VENOUS DRAINAGE OF ESOPHAGUS

The venous drainage of the esophagus is effected by tributaries that empty into the azygos and hemiazygos systems. Drainage begins in a *submucosal venous plexus*, branches of which, after piercing the muscle layers, form a venous plexus on the external surface of the esophagus. Tributaries from the cervical *esophageal veins* drain into the *inferior thyroid vein*, which empties into the right or left *brachiocephalic vein*, or into both. Tributaries from the thoracic esophageal veins on the right side join the *azygos*, *right brachiocephalic*, and, occasionally, *vertebral vein*. On the left side they join the *hemiazygos*, *accessory hemiazygos*, *left brachiocephalic*, and, occasionally, *vertebral vein*. Venous tributaries from the abdominal esophagus drain mostly into the hepatic portal vein by way of the *left gastric vein*, and to a lesser degree, the *short gastric veins*. A small amount of venous blood from the abdominal esophagus may drain to the *left inferior phrenic vein* before joining the inferior vena cava directly or via the suprarenal and then left renal vein.

The composition and arrangement of the azygos system of veins are extremely variable. The *azygos vein* arises in the abdomen from the *ascending right lumbar vein* that receives the first and second lumbar and the subcostal veins. It may arise directly from the inferior vena cava or have connections with the right common iliac, or renal, vein. In the thorax it receives the right posterior intercostal veins from the fourth to the eleventh spaces and terminates by entering the right side of the superior vena cava. The highest intercostal vein from the first space drains into the right brachiocephalic or, occasionally, into the vertebral vein. The veins from the second and third spaces unite in a common trunk (*right superior intercostal*) that ends in the terminal arched portion of the azygos. The *hemiazygos vein* arises as a continuation of the *left ascending lumbar* or from the *left renal vein*. It receives the left subcostal vein and the intercostal veins from the 8th or 9th to the 11th spaces and then crosses the vertebral column posterior to the esophagus to join the azygos. The *accessory hemiazygos vein* receives the intercostal veins from the fourth to the seventh or eighth spaces and then crosses the spine posterior to the esophagus to join the hemiazygos or to end separately in the azygos. Above, it may communicate with the left superior intercostal that drains the second and third spaces and ends in the left brachiocephalic. Drainage of the first space is into the left brachiocephalic or vertebral vein.

Often the hemiazygos, accessory hemiazygos, and superior intercostal trunk form a continuous longitudinal venous channel, with no connections to the azygos vein on the right. On the other end of the spectrum, the azygos vein may be located along the anterior aspect of the vertebral body and veins from the left side of the thorax may drain directly to it and a hemiazygos or accessory hemiazygos vein are not formed. The left



azygos system may be reduced to a slender channel, the main left venous drainage of the esophagus and the intercostal spaces then being in the veins of the respective vertebrae. Interruptions in the left azygos system by crossing to the right azygos usually occur between the seventh and ninth intercostal veins, the most common vertebral level of crossing being T8.

At the inferior end of the esophagus, branches from the left gastric vein are continuous with the lower esophageal branches. Portal hypertension may shunt

blood into the lower esophageal branches and thereafter into the superior vena cava via the azygos and hemiazygos veins. These vessels may dilate, creating esophageal varicosities. From this same region, blood may be shunted into the splenic vein, retroperitoneal veins, and inferior phrenic vein of the diaphragm, reaching the caval system. Because short gastric veins pass up from the splenic to the cardioesophageal end of the stomach, thrombosis of the splenic vein may readily lead to esophageal varices and fatal hemorrhages.

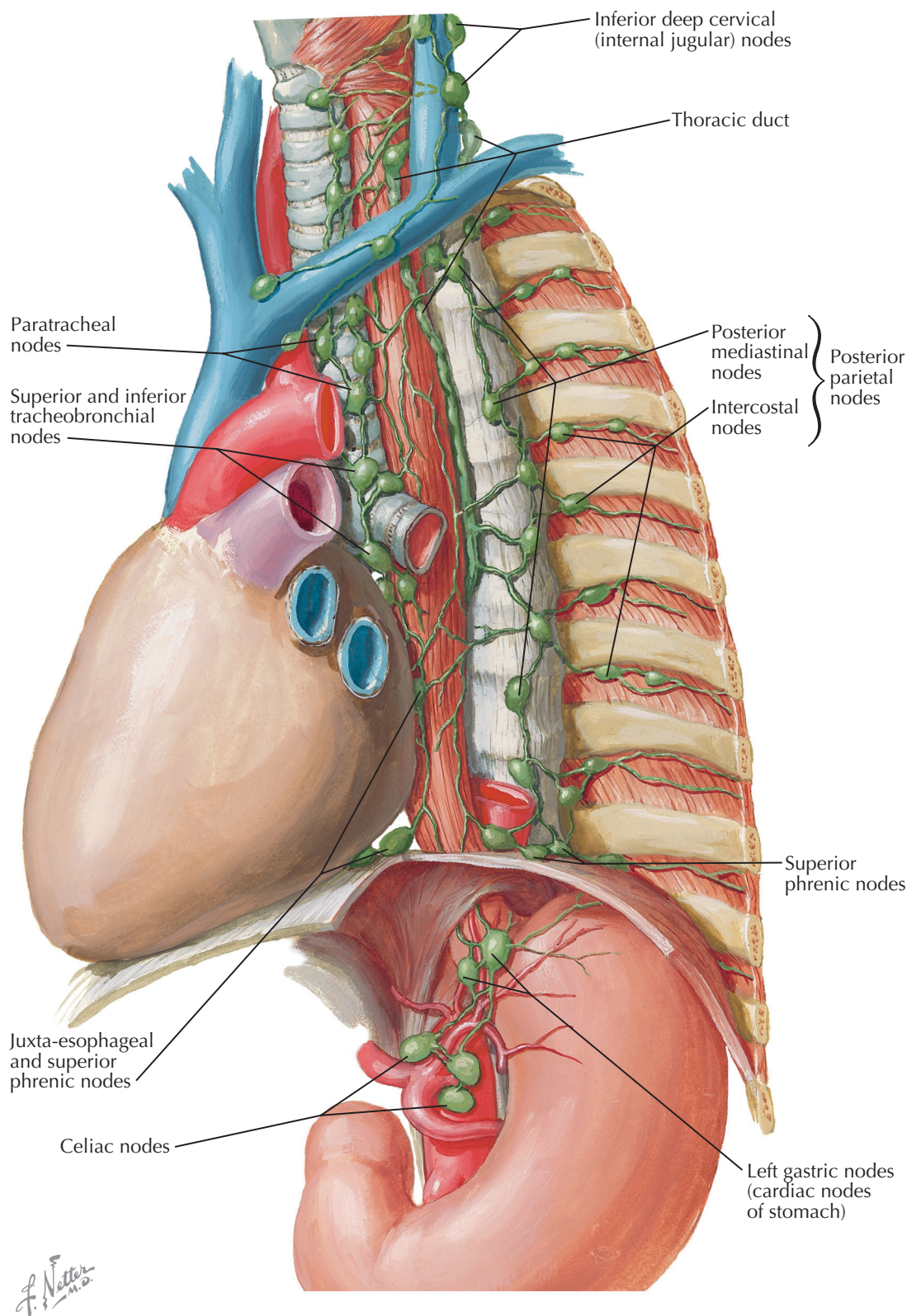
LYMPHATIC DRAINAGE OF ESOPHAGUS

The esophagus contains a rich network of lymphatic vessels, largely in the lamina propria of the mucosa but also in the other layers.

From the cervical esophagus, lymph vessels course chiefly to the *inferior deep cervical (internal jugular) lymph nodes* and possibly also to the nearby *paratracheal nodes* situated in the groove between the esophagus and trachea. The *internal jugular lymph nodes*, a subdivision of the deep cervical nodes, lie along the internal jugular vein, stretching from the parotid gland to the clavicle. On the left side, they drain to the thoracic duct and on the right to the short right lymph duct, which opens into the right subclavian vein at the angle formed by the latter with the internal jugular vein.

From the thoracic esophagus, lymphatic fluid drains posteriorly to the *posterior mediastinal* and *intercostal lymph nodes*. The *posterior parietal nodes* are formed of the posterior mediastinal and intercostal nodes. The posterior mediastinal nodes lie alongside the vertebral column, and the intercostal nodes are in the nearby intercostal spaces. Both these groups drain generally superiorly and eventually empty into the thoracic duct or into the right lymph duct, which terminates at the right subclavian vein, where it joins the right jugular vein. The *superior phrenic nodes* near the posterior esophagus are closely associated with the posterior parietal nodes, to which they drain. Anteriorly, the thoracic esophagus drains to the *paratracheal*, *superior tracheobronchial*, and *inferior tracheobronchial lymph nodes*; more inferiorly, lymphatic fluid drains to *juxtaesophageal* and *superior phrenic lymph nodes* before flowing superiorly.

The *paratracheal nodes* form a chain on each side alongside the trachea along the course of the recurrent nerves. The superior and inferior tracheobronchial nodes are the group that is situated about the bifurcation of the trachea and in the angle formed by the bifurcation. These lymph nodes may be responsible for the formation of traction diverticula when they become fibrosed as a result usually of tuberculous involvement. The tracheal and tracheobronchial nodes drain superi-



orly and usually form on each side a bronchomediastinal trunk, which, in turn, joins either the thoracic duct or the right lymph duct. They may, however, also have independent openings into the veins or may unite with the internal thoracic chain or a low node of the internal jugular chain.

From the short abdominal portion of the esophagus, lymphatic drainage is similar to that from the upper portion of the lesser curvature of the stomach, chiefly to the *cardiac nodes of the stomach*, which are a subdivision

of the *left gastric lymph node group*. From here, in turn, drainage is to the *celiac lymph nodes*. Some lymph vessels from this region also pass superiorly through the esophageal hiatus of the diaphragm and connect with the vessels and nodes above the diaphragm. Drainage from the left gastric nodes is along the course of the left gastric artery and coronary vein to the celiac nodes situated on the aorta in relation to the root of the celiac trunk. These nodes, in turn, empty into the cisterna chyli or the thoracic duct.

INNERVATION OF ESOPHAGUS

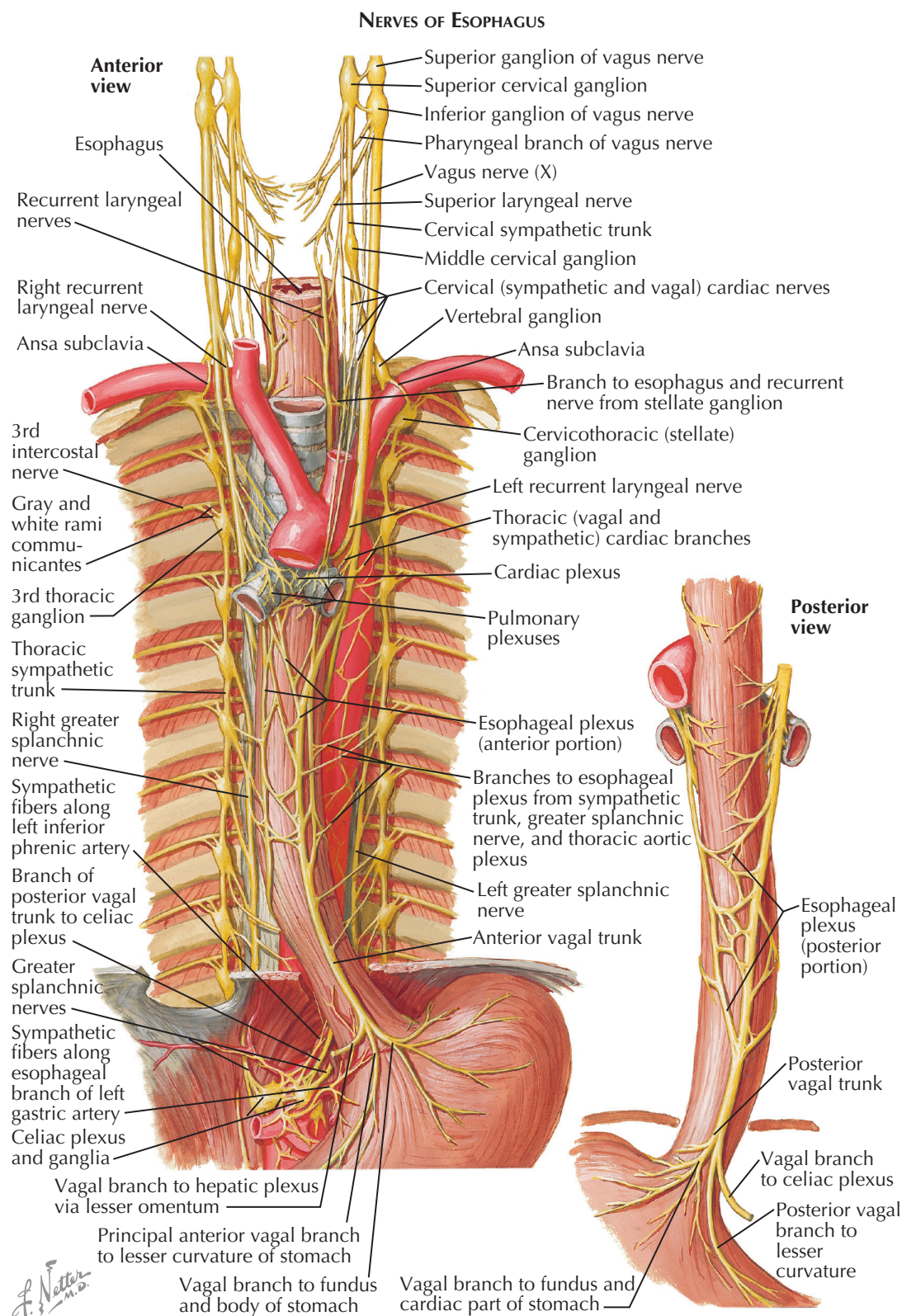
The esophagus is innervated by the vagus nerve as well as several sympathetic nerves. The vagus nerve innervates the glands and muscles of the esophagus, and the sympathetic input primarily innervates the capillary sphincters associated with the organ's blood supply.

VAGUS NERVE (SOMATIC AND PARASYMPATHETIC SUPPLY)

The vagus nerve conveys both motor and sensory fibers between the nuclei of the medulla oblongata and esophagus. Like the pharynx, the skeletal muscle of the upper esophagus is voluntary and the axons that innervate these fibers arise primarily from nerve cell bodies in the *nucleus ambiguus*. However, the amount of smooth muscle within the muscularis externa of the esophagus becomes more pronounced as one moves inferiorly and it is primarily innervated by axons from the *dorsal vagal motor nucleus*.

In the neck, where skeletal muscle predominates, the esophagus receives somatomotor axons from the *recurrent laryngeal nerves* that run superiorly between the esophagus and trachea. On the right side the recurrent laryngeal nerve arises from the vagus nerve at the root of the neck and turns superiorly by passing inferior to the right subclavian artery before ascending. The left recurrent laryngeal nerve arises from the left vagus nerve opposite the aortic arch and curves beneath the arch of the aorta to reach the groove between the trachea and esophagus. Some inconstant filaments pass to the esophagus from the main vagus nerves that lie in the carotid sheath behind and between the common carotid artery and internal jugular vein.

In the thorax, the esophagus receives filaments from the left recurrent laryngeal nerve and both vagus nerves. The vagus nerves descend posterior to the bronchi, giving off branches that unite with axons from the sympathetic trunk to form the smaller anterior and larger posterior pulmonary plexuses. Below the bronchi each vagus nerve usually splits into two to four branches, which apply themselves to the surface of the esophagus in the posterior mediastinum. The branches from the right and left vagus nerves rotate posteriorly and anteriorly (respectively) as they divide and reunite to form an open-meshed *esophageal plexus* containing small



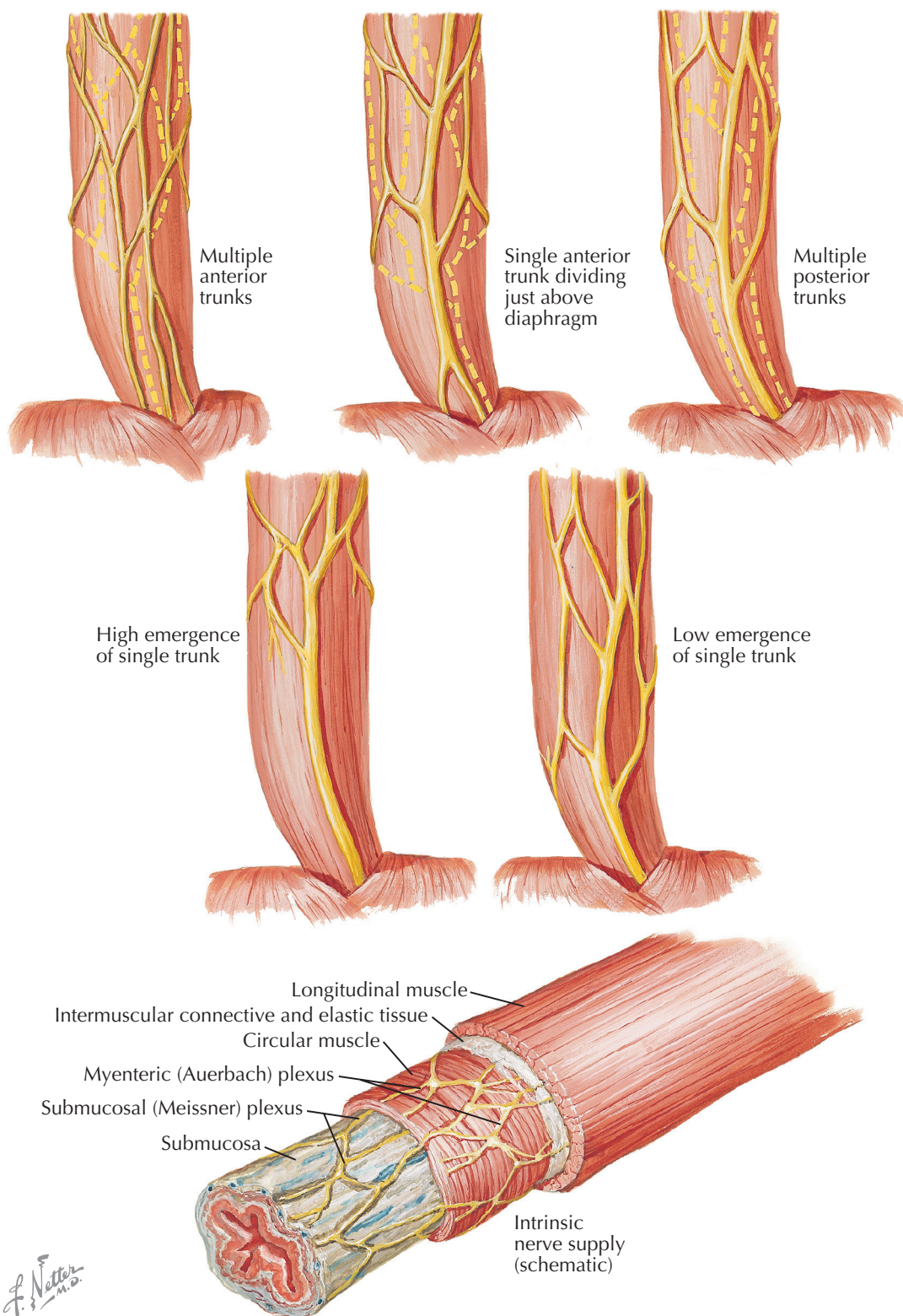
ganglia. At a variable distance above the esophageal hiatus in the diaphragm, the meshes of the plexus become reconstituted into an anterior vagal trunk and posterior vagal trunk, embedded in the anterior and posterior wall of the lowest part of the esophageal wall. Offshoots from the esophageal plexus and from the *anterior and posterior vagal trunks* sink into the esophageal wall. Common variations in the plexus and in the vagal trunks are of especial significance to anyone performing vagotomy, and the surgeon should remember

that there may be more than one anterior or posterior vagal trunk. The vagus nerves and their resultant trunks interdigitate with filaments from the sympathetic trunks so that, from the neck downward, they are really mixed parasympathetic-sympathetic plexuses.

SYMPATHETIC SUPPLY

The sympathetic preganglionic fibers are the axons that originate in the intermediolateral cell column, located

INTRINSIC NERVES AND VARIATIONS IN NERVES OF ESOPHAGUS



INNERVATION OF ESOPHAGUS

(Continued)

mainly in the fourth to sixth thoracic segments of the spinal cord. These presynaptic axons emerge in the anterior spinal nerve roots corresponding to the segments containing their parent cells. They leave the spinal nerves via *white rami communicans* and pass to the ganglionic nerve cell bodies located in the *sympathetic trunk*. Some fibers form synapses with cells in the mid-thoracic ganglia, but others pass to higher and lower ganglia in the trunk before synapsing. Postsynaptic axons exiting the sympathetic trunk reach the esophagus through branches from the sympathetic trunks. The afferent impulses are conveyed in fibers that pursue an antiparallel route, but they do not relay in the sympathetic trunk. Instead they pass through the trunk without synapsing, travel through the white rami communicans to reach the spinal nerve, and then travel along the posterior nerve roots before reaching the posterior horn of the spinal cord. Their pseudounipolar nerve cell bodies are located in the posterior (dorsal) root ganglia.

The uppermost part of the esophagus is supplied by offshoots from the pharyngeal plexus that contain postsynaptic sympathetic axons. More inferiorly, it receives axons from the cardiac branches of the *superior cervical ganglia* and occasionally from the *middle cervical* or *vertebral ganglion* of the sympathetic trunk. Other fibers reach the esophagus in the delicate nerve plexuses accompanying the arteries that supply it. In the upper thorax, esophageal axons are supplied by the *stellate ganglia* or *ansa subclavia*, and the delicate thoracic cardiac nerves are often associated with fibers for the esophagus, trachea, aorta, and pulmonary structures.

In the lower thorax, axons pass from the *greater (thoracic) splanchnic nerves* to the nearby esophageal plexus. The greater splanchnic nerves generally arise by three

or four larger roots and an inconstant number of smaller rootlets from the fifth to the ninth thoracic ganglia of the sympathetic trunk, although there is significant variation. The roots and rootlets pass obliquely anteriorly, medially, and inferiorly across the sides of the thoracic vertebral bodies and intervertebral disks and coalesce to form a nerve of considerable size. On each side the nerve enters the abdomen by piercing the homolateral diaphragmatic crus or, less often, by

passing between the lateral margins of the crura and the fibers arising from the medial arcuate ligament. The intraabdominal course is short, and each nerve breaks up into branches that end mainly in the celiac ganglion. The lesser and least thoracic splanchnic nerves terminate mainly in the aorticorenal and superior mesenteric ganglia. Filaments from the terminal part of the left greater splanchnic nerve reach the abdominal part of the esophagus.

INTRINSIC INNERVATION OF ALIMENTARY TRACT

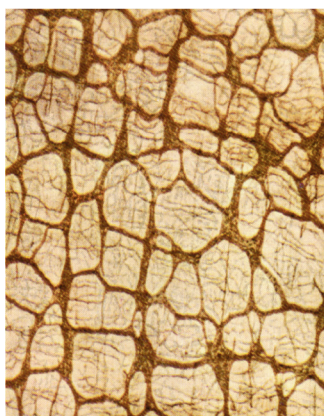
From the esophagus to the rectum, the intrinsic innervation of the alimentary tract is effected through the enteric nervous system. This network is composed of numerous ganglion cells interconnected by their axons and dendrites. They are found primarily in two locations, between the longitudinal and circular layers of the muscularis externa, as the *myenteric (Auerbach) plexus*, and between the muscularis externa and the submucosa, as the *submucosal (Meissner) plexus*. The former is relatively coarse, and its meshes consist of thick, medium, and thin bundles of fibers, which are described as its primary, secondary, and tertiary parts. The submucosal plexus is more delicate. Other subsidiary plexuses have been described, such as a rarefied subserous plexus in those parts of the alimentary canal covered by peritoneum, but minute details of these need not be given.

The *enteric plexuses* vary in pattern and density in different parts of the alimentary tract and in different species of animals. They are well developed in the regions from the stomach to the lower end of the rectum and are less well formed in the esophagus, particularly in its upper half, which is primarily skeletal muscle. The ganglion cells are also not distributed uniformly; thus, the density of cell distribution in the myenteric plexus is lowest in the esophagus, rises steeply in the stomach until it reaches its peak at the pylorus, falls to an intermediate level throughout the small intestine, and then increases again along the colon and especially in the rectum. The density of cell population in the submucosal plexus seems to run roughly parallel to that in the myenteric plexus.

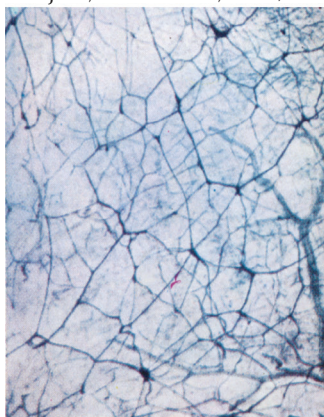
The enteric plexuses contain postsynaptic sympathetic axons, as well as presynaptic and postsynaptic parasympathetic axons. These exist alongside afferent axons from the alimentary tract, and the intrinsic ganglia of each plexus. Vagal presynaptic fibers form synapses with the ganglion cells whose axons are the postsynaptic parasympathetic fibers. The sympathetic presynaptic fibers have already relayed in paravertebral or prevertebral ganglia, and so the sympathetic fibers in the plexuses pass through to their terminations without synaptic interruptions. The afferent fibers from the esophagus, stomach, and duodenum are carried to the brainstem and cord through the vagal and sympathetic nerves supplying these parts, but they form no synaptic connections with the ganglion cells in the enteric plexuses.

Two chief forms of nerve cells, types I and II, occur in the enteric plexus. *Type I cells* are *multipolar* and confined to the myenteric plexus, and their dendrites branch close to the parent cells. Their axons run for varying distances through the plexuses to establish synapses with *cells of type II*, which are more numerous and are found in both myenteric and submucosal plexuses. Most type II cells are multipolar, and their longer dendrites proceed in bundles for variable distances before ramifying in other cell clusters. Many of their axons pass outward to end in the muscle coats, and others proceed inward to supply the muscularis mucosae and to ramify around vessels and between epithelial secretory cells; their distribution suggests that they are motor or secretomotor in nature.

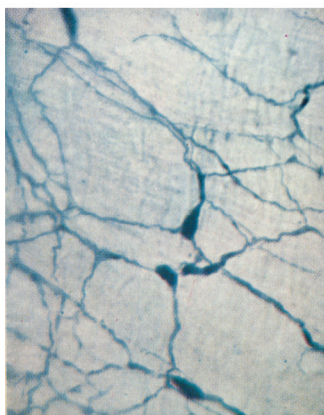
Another group of cells in the area are the *interstitial cells of Cajal*, which are associated with the terminal networks of all autonomic nerves and act as pacemaker



1. Myenteric plexus (Auerbach) lying on longitudinal muscle coat. Fine tertiary bundles crossing meshes (duodenum of guinea pig, Champy-Coujard, osmic stain, $\times 20$)



2. Submucosal plexus (Meissner) (ascending colon of guinea pig. Stained by gold impregnation, $\times 20$)



3. Interstitial cells of Cajal forming part of dense network between muscle layers (descending colon of guinea pig. Methylene blue, $\times 375$)

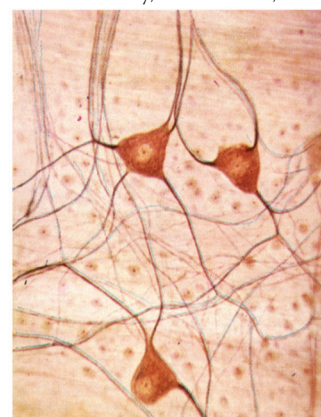


Relative concentration of ganglion cells in myenteric (Auerbach) plexus and in submucosal (Meissner) plexus in various parts of alimentary tract (myenteric plexus cells represented by maroon, submucous by blue dots)

Photomicrographs kindly provided by Dr. J. R. Rintoul and Mr. P. Howarth, Manchester University, England.



4. Multipolar neuron, type I (Dogiel), lying in ganglion of myenteric (Auerbach) plexus (ileum of monkey. Bielschowsky, silver stain, $\times 375$)



5. Group of multipolar neurons, type II, in ganglion of myenteric (Auerbach) plexus (ileum of cat. Bielschowsky, silver stain, $\times 200$)

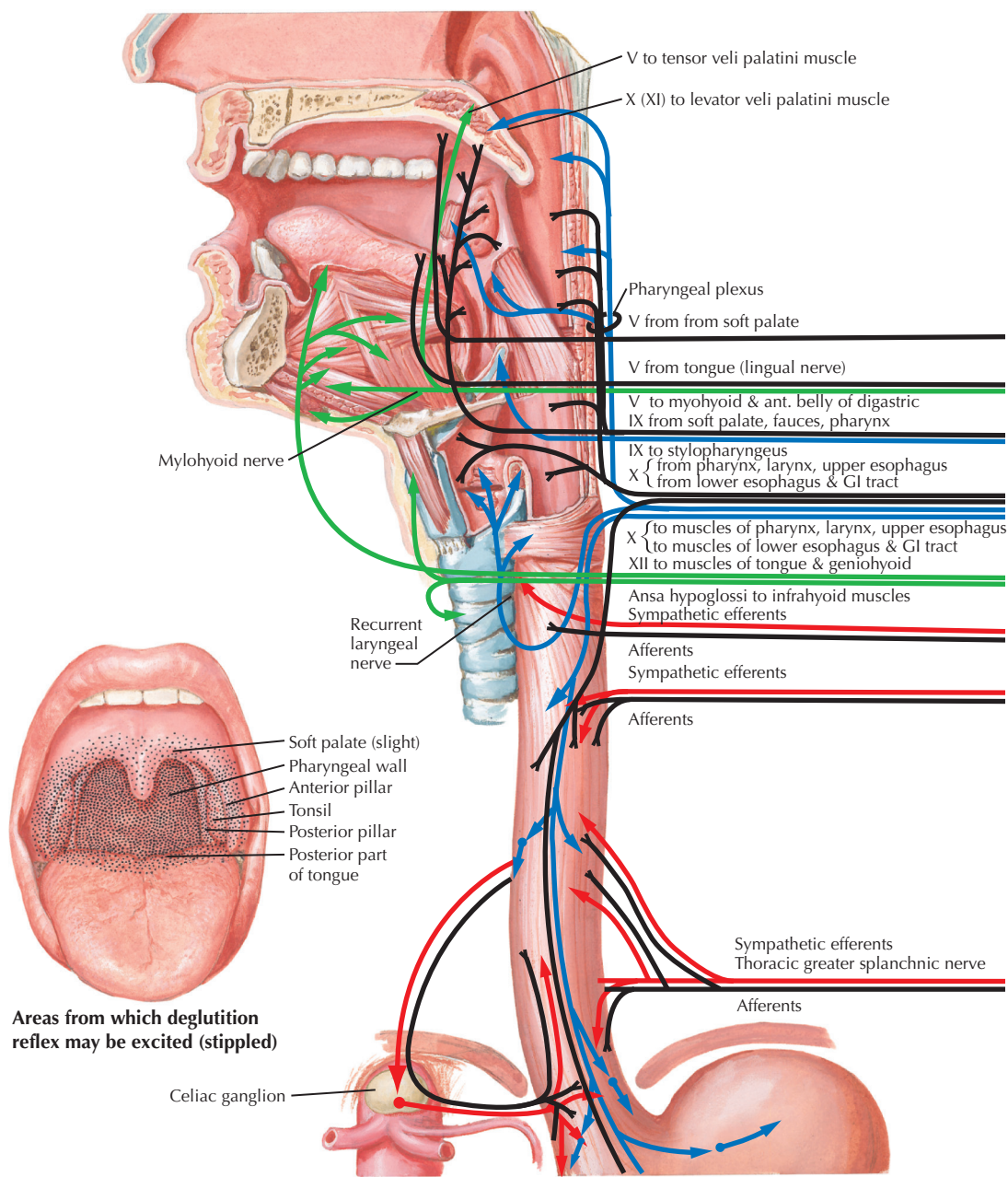


6. Pseudo-unipolar neuron within ganglion of myenteric plexus (ileum of cat. Bielschowsky, silver stain $\times 375$)

cells of the smooth muscle layers of the gastrointestinal tract. The frequency of this pacemaker activity varies between different organs. Under experimental conditions peristaltic movements occur in isolated portions of the gut, indicating the importance of the intrinsic neuromuscular mechanism, but the parasympathetic and sympathetic nerves regulate the activity of the gut tube. Local reflex arcs may exist in the enteric plexuses; this possibility is supported by the observation that in addition to type I and II multipolar cells, much smaller

numbers of pseudounipolar and bipolar cells can be detected in the submucosa, potentially acting as the afferent links in local reflex arcs.

In congenital megacolon (Hirschsprung disease) the enteric plexuses are apparently undeveloped or degenerated over a segment of the alimentary tract, although the extrinsic nerves are intact. The affected segment is tonically contracted and peristaltic movements are defective or absent. This results in distention of the proximal region of the gastrointestinal tract.

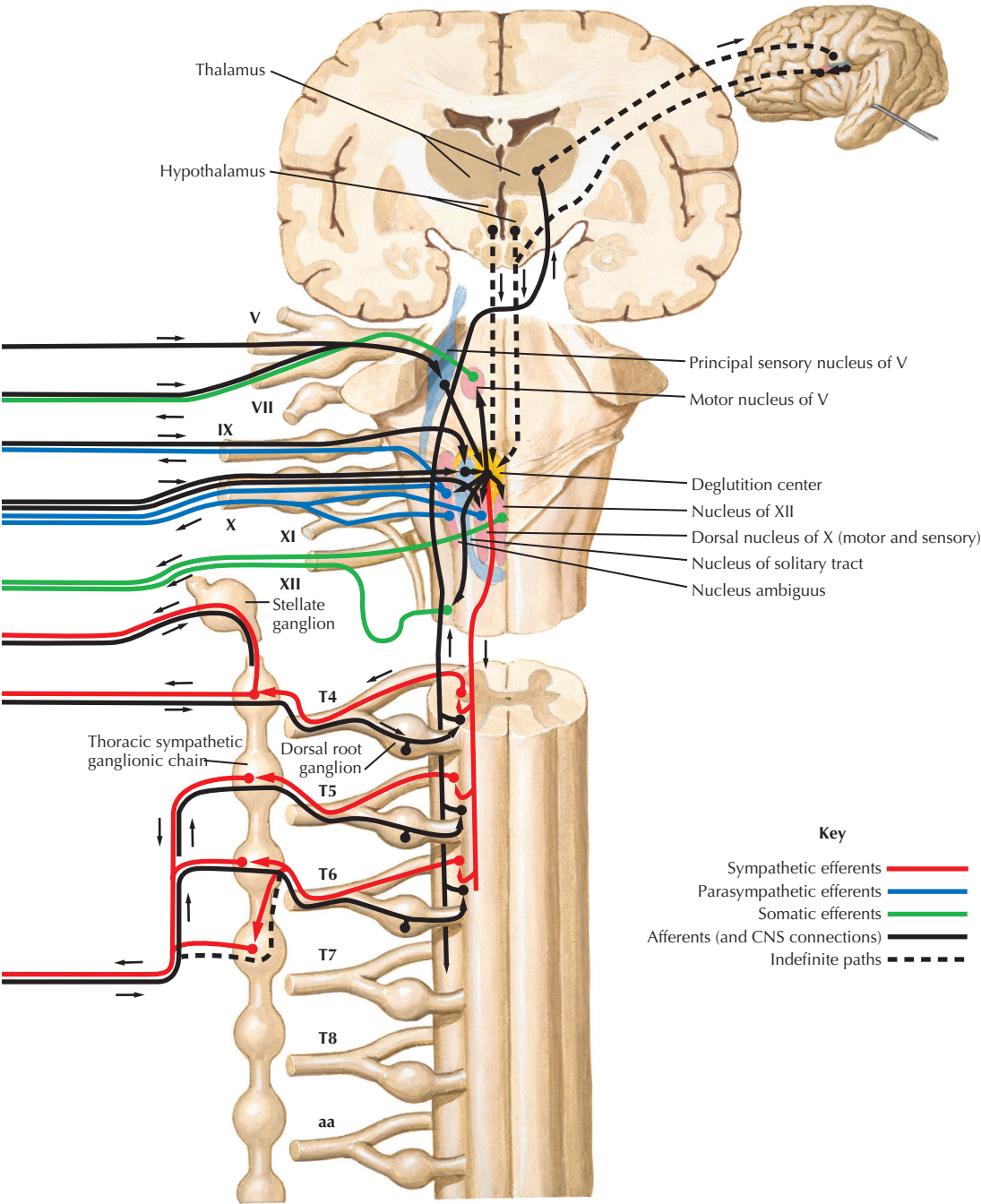


NEUROREGULATION OF DEGLUTITION

The main center for control of motility in the esophageal body and lower esophageal sphincter is the *myenteric plexus*. This plexus is located between the layers of the outer longitudinal and inner circular muscle of the muscularis propria. As the esophagus changes proximally from striated to smooth muscle distally, the

myenteric plexus exhibits greater control over motor function. The plexuses connect to fibers of the vagus nerve which provide modulatory function. In the proximal esophagus, central control through these vagal fibers originates in the nucleus ambiguus whereas vagal fibers for the smooth muscle esophagus originate from the dorsal motor nucleus, both in the brainstem. The vagus nerves also carry sensory nerves originating from the muscle and the mucosa. In the cervical esophagus, efferent fibers of the vagus course through the recur-

rent laryngeal nerve. The thoracic esophagus receives fibers directly off the vagus. Afferent fibers course through the superior and recurrent laryngeal nerve and the vagus. Peristalsis with aboral movement of the bolus from the proximal esophageal segment into the stomach is the main function of the esophagus. Primary peristalsis is initiated with pharyngeal contraction, whereas secondary peristalsis occurs in response to esophageal distention and originates from the point of stimulation.



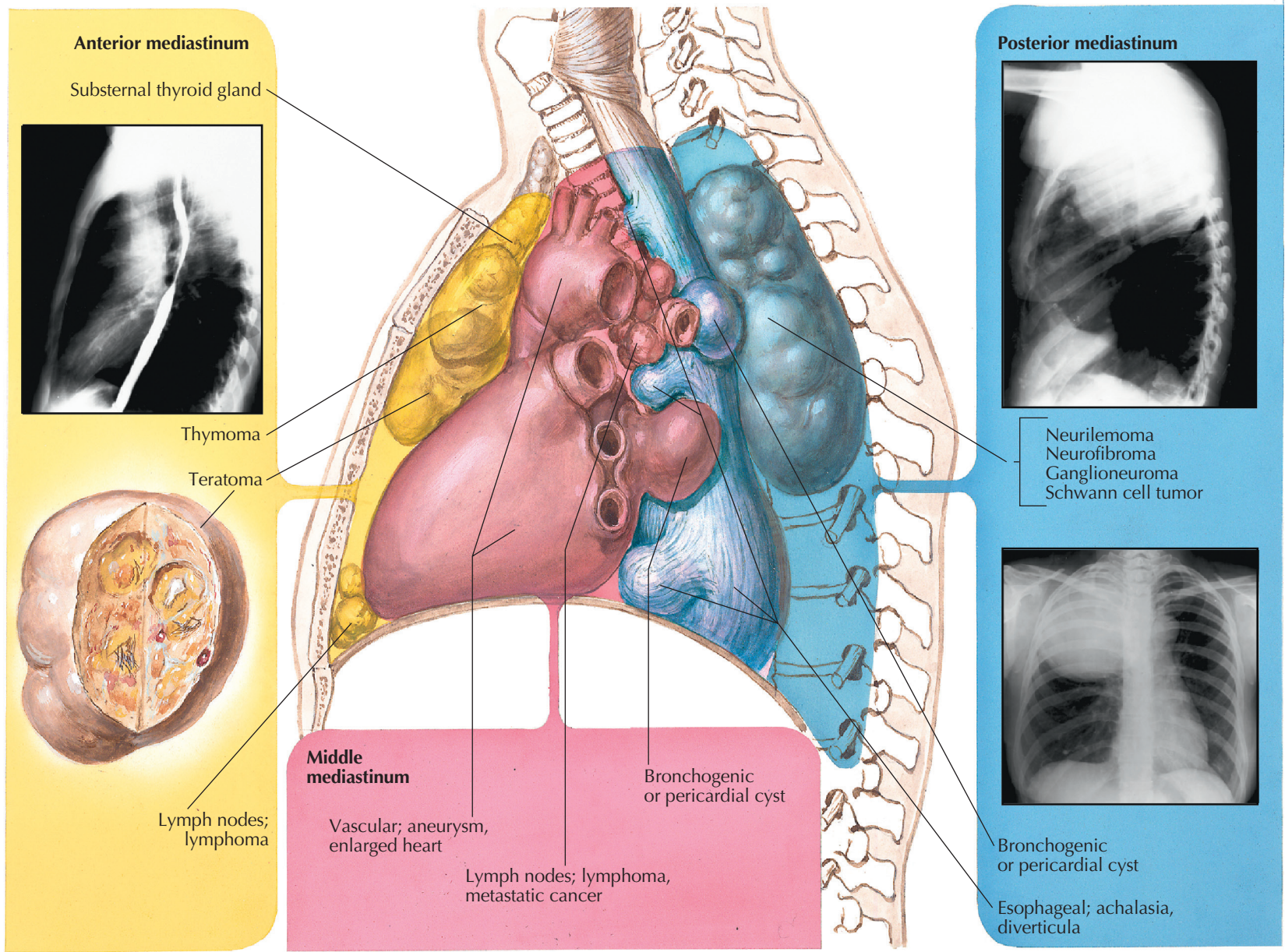
F. Netter M.D.

NEUROREGULATION OF DEGLUTITION *(Continued)*

This latter type of peristalsis is particularly important in clearing a reflux of gastric content. Peristalsis is coordinated by the neural network to achieve a pattern of descending proximal segment contraction to propel the bolus and distal segment relaxation to receive the bolus. This reflex is achieved through coordinated release

of excitatory neuropeptides proximally and inhibitory neuropeptides distally. Excitatory peptides in the esophagus include acetylcholine contained by neurons more proximally and nonadrenergic noncholinergic neurons distally. Nitric oxide and vasoactive intestinal peptide are the major inhibitory neuropeptides contained in neurons. Descending coordination is achieved through a combination of local, myenteric, and central vagal control. Concordant with peristalsis, coordinated opening of the gastroesophageal high-pressure zone must occur

to complete bolus propulsion into the stomach. This involves the neural coordination of the two structures that form the lower esophageal sphincter (LES), the intrinsic LES and the crural diaphragm. The intrinsic LES maintains a baseline tone likely through both cholinergic and adrenergic activity. Similar to the esophageal body, the bulk of control is local through the myenteric plexus but can be modulated by vagal reflexes, particularly in reaction to modifying events such as increased abdominal strain. Crural diaphragm contraction is mediated through the phrenic nerve.

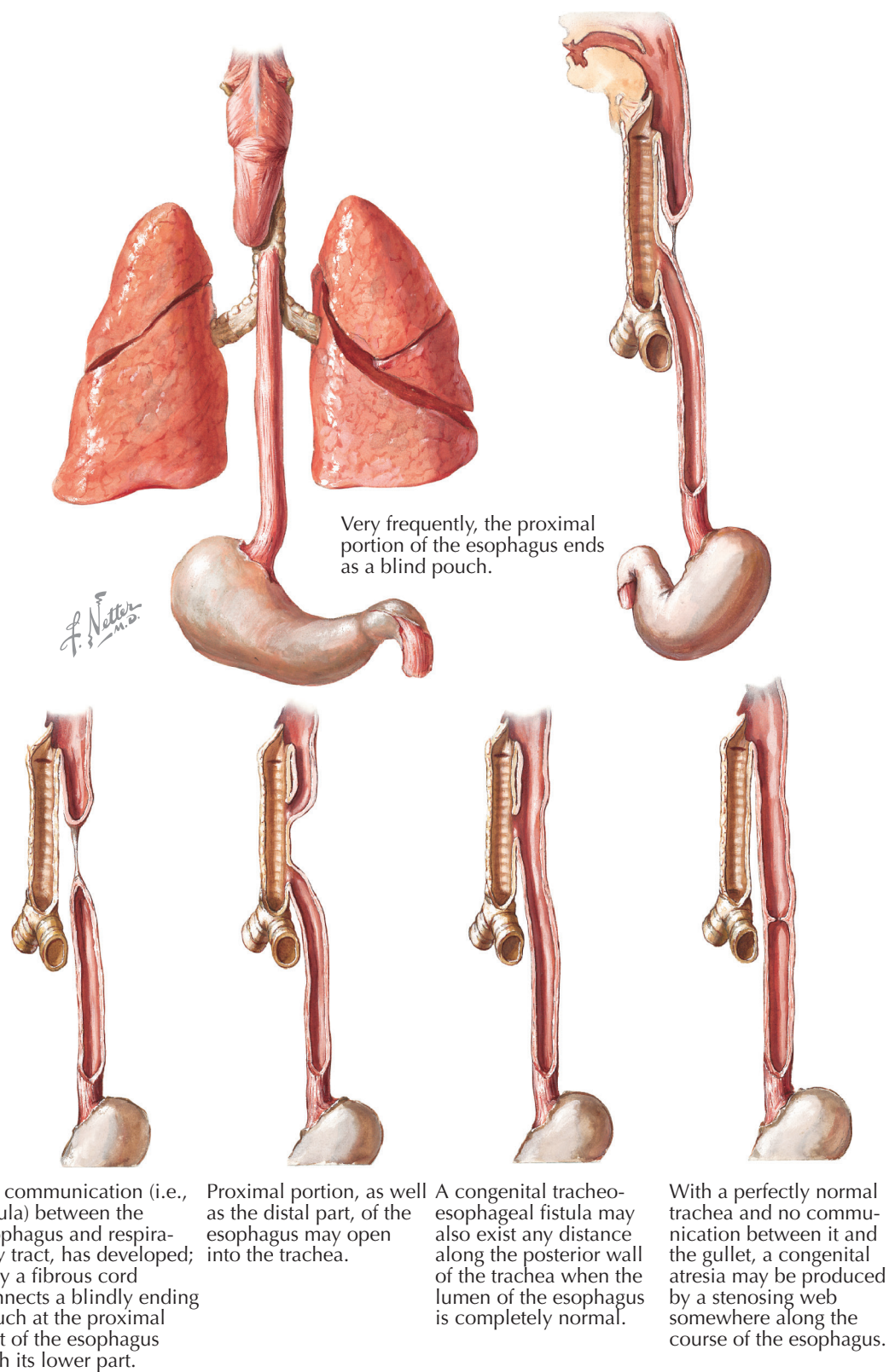


ESOPHAGEAL DUPLICATION CYSTS

Esophageal duplication cysts are rare congenital anomalies, although the esophagus is the second most common location for duplication in the gastrointestinal tract after the ileum. The cysts are most frequently located in the right posterior mediastinum at the level of the distal third of the esophagus. The cysts are lined

by squamous, columnar, cuboidal, pseudostratified, or ciliated epithelium. They are covered by two thick muscle layers that are in contiguity with the muscularis propria. They may occur with other congenital abnormalities such as esophageal atresia. Duplication may present with megaesophagus similar to achalasia due to obstruction at the gastroesophageal junction by the cyst. Rarely, cancer may develop in the cyst. The most common presenting symptoms are dysphagia or respiratory symptoms (particularly in the proximal

esophagus) due to esophageal and or tracheobronchial compression. Imaging is commonly performed through a combination of techniques, including endoscopy, endoscopic ultrasound (particularly when the cyst appears solid), computed tomography, and barium esophagography. The diagnosis can be made in utero, in childhood, or in adulthood. When found incidentally, no further treatment is needed. For patients with symptoms or complications, surgical excision is usually indicated.

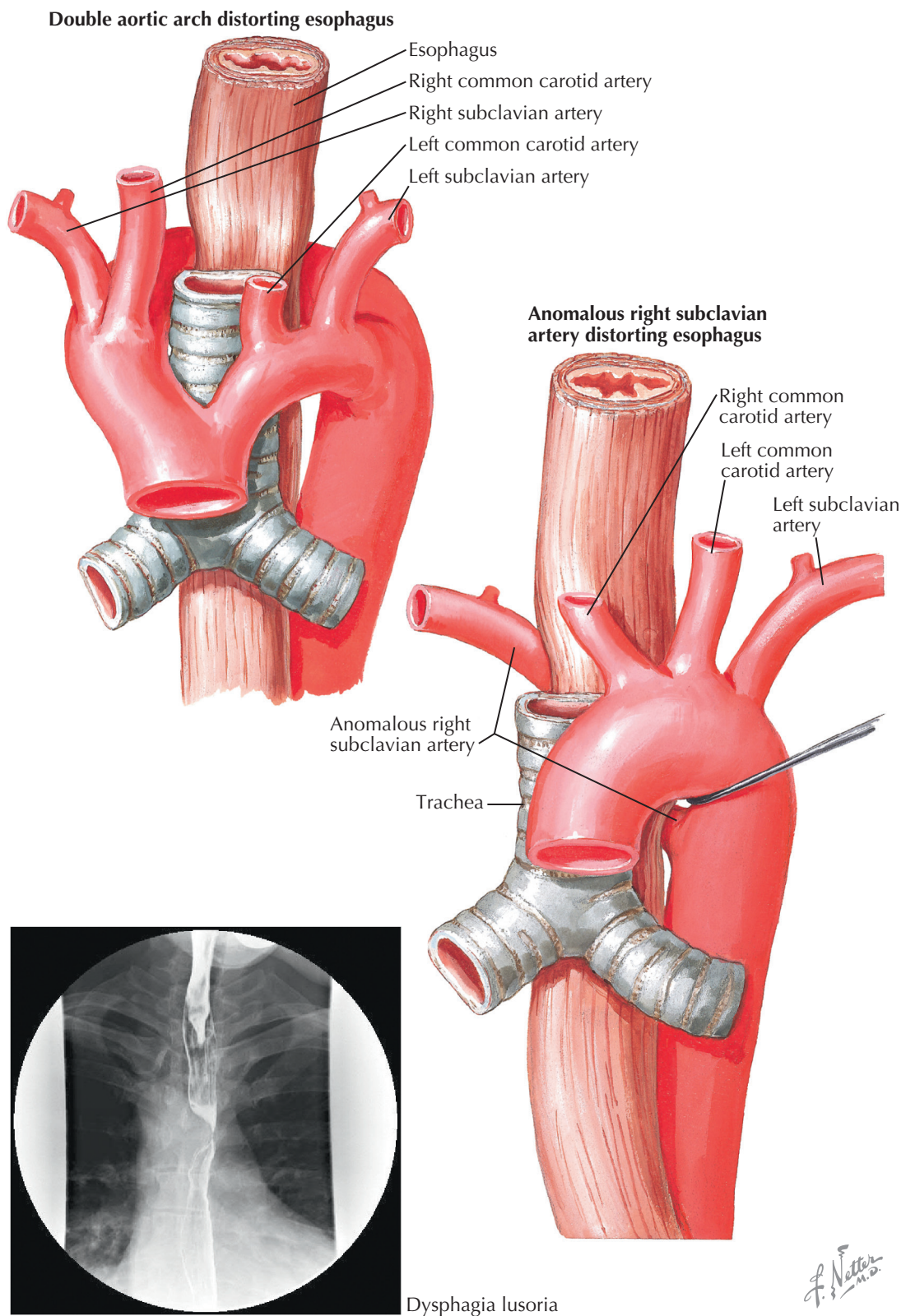


CONGENITAL ESOPHAGEAL STENOSIS

Congenital esophageal stenosis (CES) is a rare clinical condition found in 1 in 25,000 to 50,000 live births, although the true incidence remains unknown. CES is characterized by an intrinsic circumferential narrowing of the esophageal lumen that is present at birth, although not necessarily symptomatic in the neonatal

period. Its etiology remains unknown, but an embryologic origin has been suggested. There are three histologic types of CES: ectopic tracheobronchial remnants in the esophageal wall, segmental fibromuscular hypertrophy of the muscle and submucosal layers, and a membranous diaphragm or stenosis. CES is frequently associated with esophageal atresia. CES is found equally in male and female children and is typically diagnosed before the age of 14, most commonly by 2 years. The most common presenting symptoms are dysphagia,

food impaction, and respiratory symptoms. The stenosis may also be found incidentally. The diagnosis is typically made by barium swallow and/or endoscopy with the visualization of cartilaginous remnants. The ringlike appearance may cause confusion with eosinophilic esophagitis. Some patients may be effectively treated with esophageal dilation, though surgical therapy with resection is commonly required, particularly if the stenosis occurs in association with esophageal atresia.



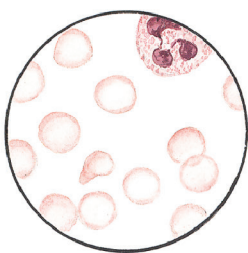
DYSPHAGIA AORTICA AND VASCULAR COMPRESSION

Dysphagia aortica is a heterogeneous group of disorders that results from an aortic aneurysm(s) causing external compression of the esophagus and typically causing dysphagia. Etiologies of the aneurysms leading to dysphagia include atherosclerotic vascular disease, trauma, infections such as syphilis or fungus, and autoimmune diseases such as Takayasu arteritis. Most aneurysms causing dysphagia have been described in the descending aorta. Primary therapy is often directed toward the aneurysm and may include esophageal or aortic mobilization, stenting, and dilation. When the patient has significant cardiovascular risks, commonly

associated with aneurysms, therapy is supportive, with dietary changes to soft solids and liquids. Notably, similar presentations may occur with esophageal compression from other vascular structures, such as a dilated right atrium in patients with chronic heart failure or mitral stenosis. Another cause of esophageal vascular compression is *dysphagia lusoria* (freak of nature). There are two congenital conformations of dysphagia lusoria. In the first, a right subclavian artery located on the left side of the

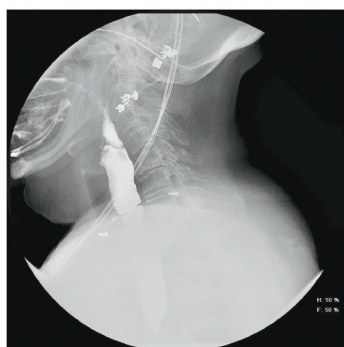
aortic arch crosses over behind the esophagus to supply the right upper extremity. The second type involves an aberrant left subclavian artery from the right side of the aorta that crosses left to right behind the aorta. Both make a transverse impression on the esophageal wall and can be confirmed by magnetic resonance or computed tomography angiography. In most patients, the abnormalities are found incidentally and the association with dysphagia is tenuous. In rare situations, surgery is needed.

Plummer-Vinson syndrome

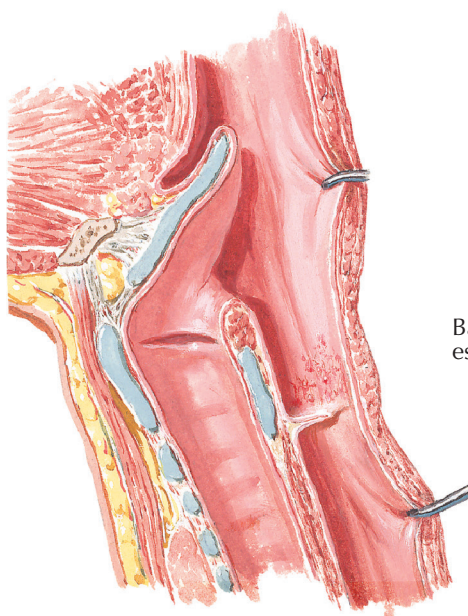
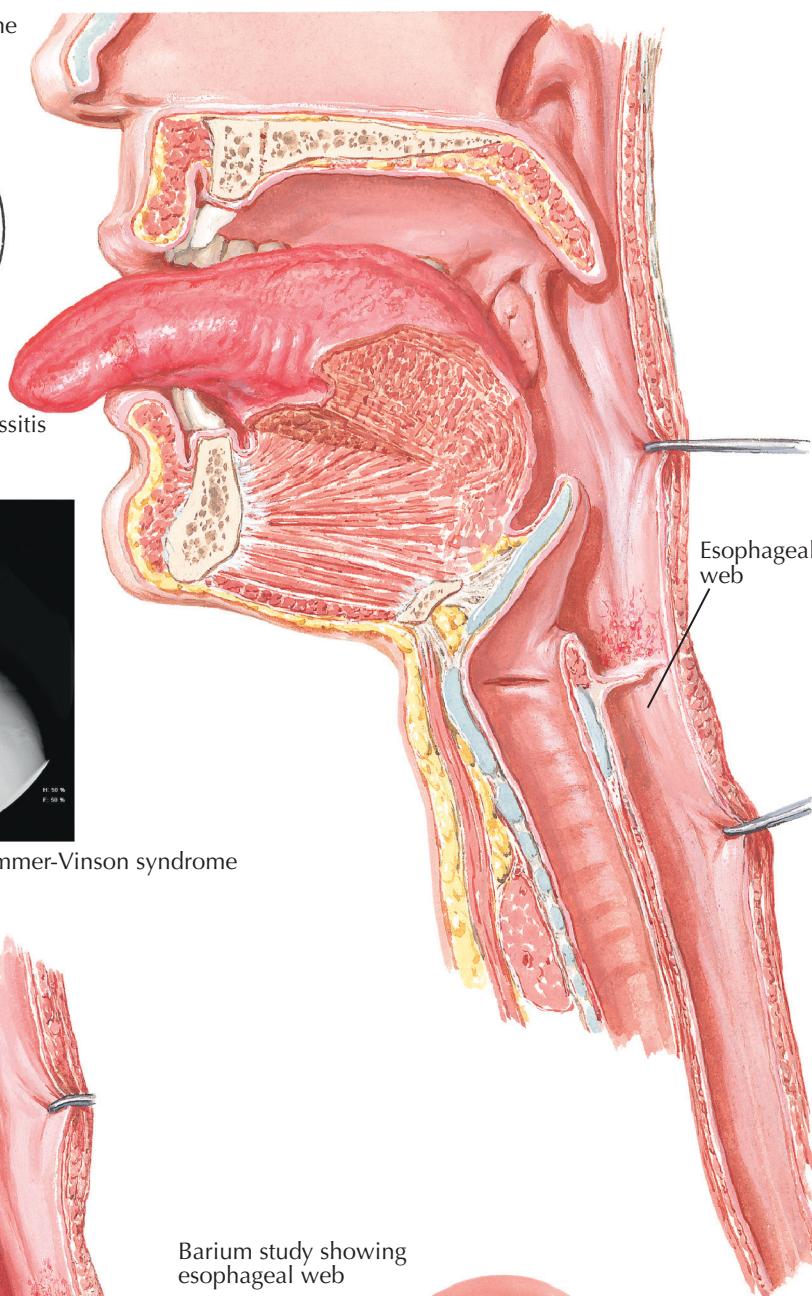


Hypochromic anemia

Glossitis



Esophageal web with Plummer-Vinson syndrome



Simple esophageal web without other manifestations of Plummer-Vinson syndrome

Barium study showing esophageal web



Web: Esophagoscopic view

F. Netter M.D.

PLUMMER-VINSON SYNDROME

Plummer-Vinson syndrome (also termed Paterson-Kelly syndrome) is an uncommon disorder manifested by a constellation of findings, including iron deficiency anemia and proximal cervical esophageal webs. It is most typically found in middle-aged women. The precise relationship of the webs to the anemia is unclear.

The chief characteristic of Plummer-Vinson syndrome is dysphagia, which is often accompanied by *hypochromic anemia*.

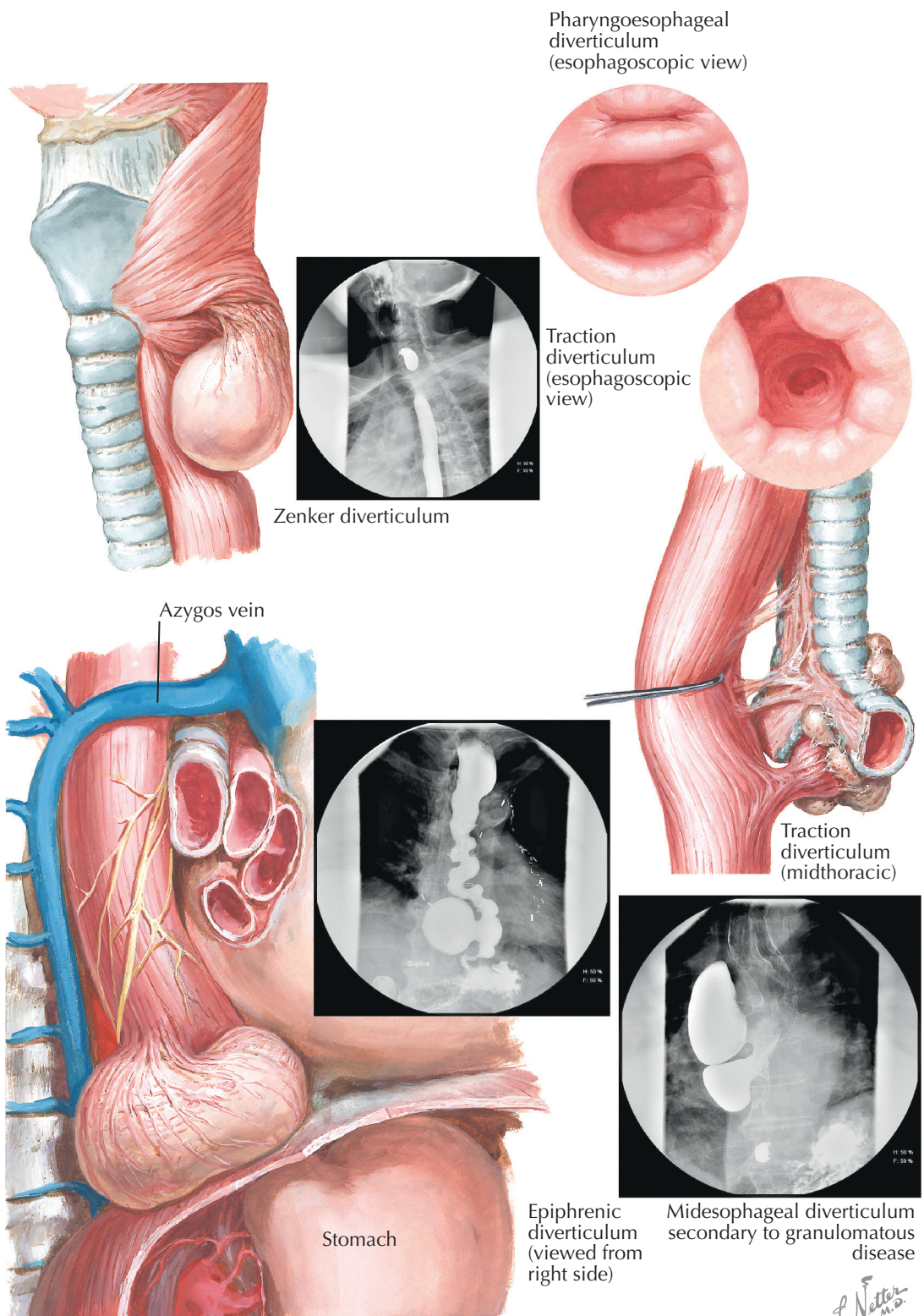
The patient's chief complaints are invariably difficulty in swallowing, usually accompanied by generalized weakness due to anemia, and dryness of the mouth

with burning of the tongue. The syndrome develops gradually over a period of several months or even years and leads to a sensation of obstruction in the back of the throat and neck. Fluids are in almost all cases well tolerated, whereas solid food may be rejected or impossible to swallow.

Atrophic glossitis and a dry pharyngeal and buccal mucosa, with painful cracks at the angles of the mouth, are present regularly in all patients suffering from this

syndrome. The atrophic mucosa may extend into the hypopharynx and into the mouth of the esophagus. Less common are the brittle fingernails and other evidence of multiple avitaminosis.

Older case reports have demonstrated resolution of the webs with correction of the iron deficiency and recurrence without correction. Treatment is generally dilation or endoscopic incision of the web and correction of the iron deficiency anemia.



DIVERTICULA OF ESOPHAGUS

Diverticula may form at any point along the length of the esophagus. The pathogenesis of the diverticula is usually either *pulsion* (due to high intrinsic esophageal pressure secondary to a motility disorder) or *traction* secondary to a process extrinsic to but neighboring the esophagus that tethers to and pulls the esophageal wall away from the lumen. In the proximal esophagus, a *pulsion Zenker diverticulum* may form. This outpouching occurs in a mechanistically weak area of the pharynx located posteriorly between the inferior pharyngeal constrictor and the cricopharyngeus muscles (triangle of Killian). The source of pulsion forces is felt to be contraction of the pharynx against a fibrotic, poorly compliant cricopharyngeus. Treatment is myotomy of the cricopharyngeus to prevent re-formation with

diverticulectomy, diverticulopexy, or division, depending on the size of the diverticulum. In the midesophagus, traction diverticula are more common. These typically occur from external tethering forces, such as mediastinal adenopathy involved with cancer or with granulomatous infection, such as tuberculosis or histoplasmosis. The openings of the outpouchings tend to be broader, without acute entry into the esophagus when compared with the pulsion type. Nonspecific diverticula, possibly due to pulsion, may also form in

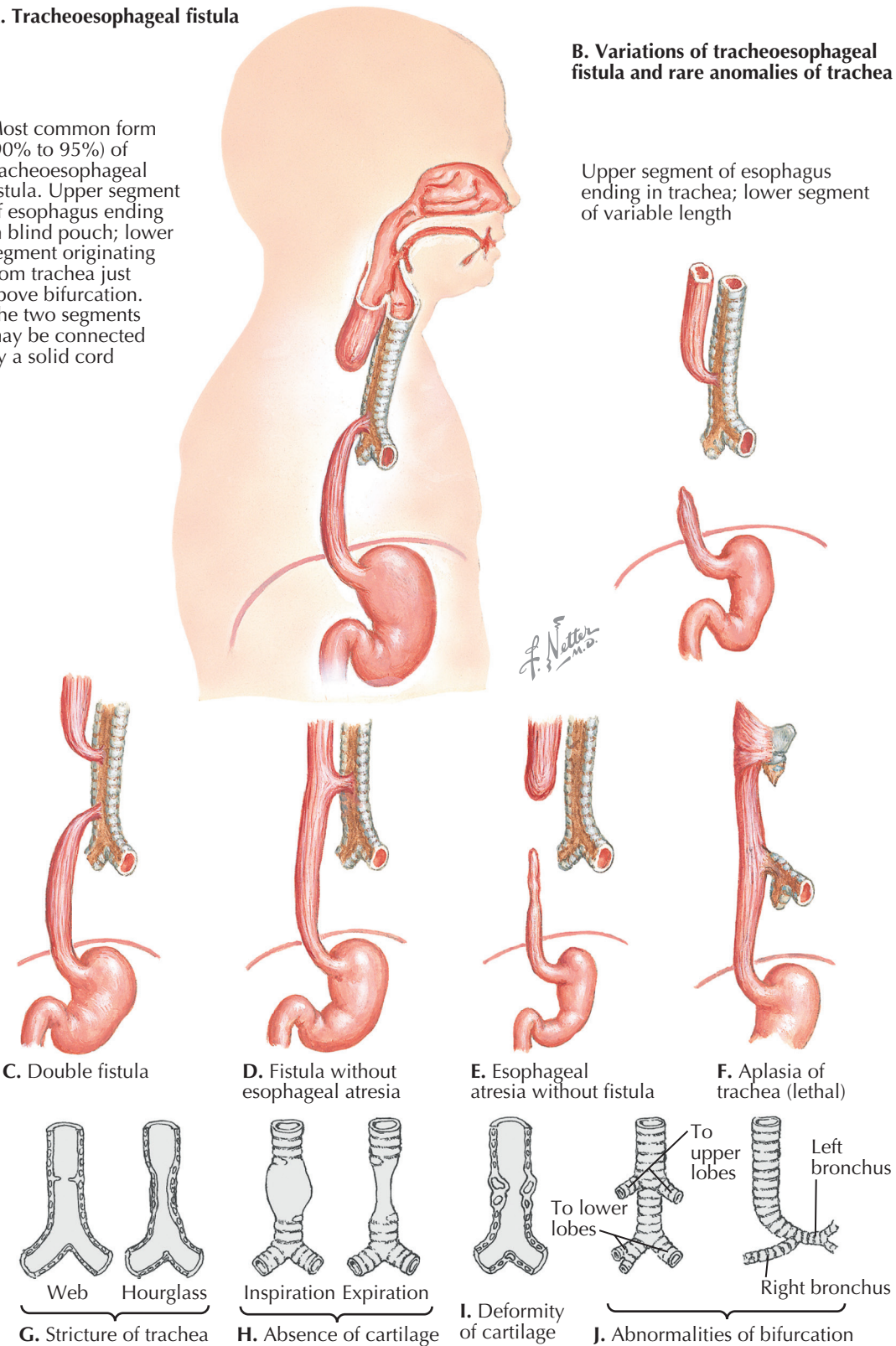
the midesophagus, often incidentally and sometimes causing symptoms. The precise etiology is unclear. A distal esophageal epiphrenic diverticulum is typically caused by pulsion and forms proximal to the gastroesophageal junction. It generally results from a hypertensive lower esophageal sphincter with or without changes of achalasia. Similar to treatment of a Zenker diverticulum, a myotomy of the high-pressure zone must be performed, in addition to diverticulectomy for large sacs.

A. Tracheoesophageal fistula

Most common form (90% to 95%) of tracheoesophageal fistula. Upper segment of esophagus ending in blind pouch; lower segment originating from trachea just above bifurcation. The two segments may be connected by a solid cord

B. Variations of tracheoesophageal fistula and rare anomalies of trachea

Upper segment of esophagus ending in trachea; lower segment of variable length



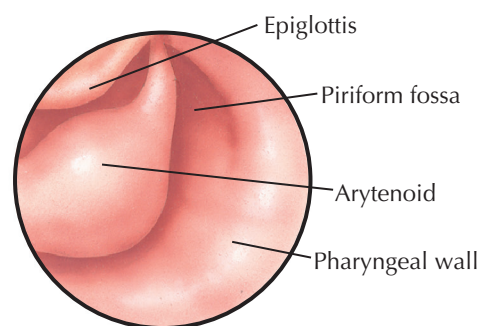
ESOPHAGEAL ATRESIA

Esophageal atresia is a sporadic congenital disease of varied anatomic presentation defined by atresia and/or fistulization of the esophagus to the trachea. It is the most common congenital abnormality of the esophagus but presents only in 1:2500 to 1:4500 births. The type of esophageal atresia is classified on the basis of specific anatomic patterns and the frequency of occurrence. The etiology is unclear, with several theories proposed, generally involving abnormal formation of a tracheal diverticulum during embryogenesis. Genetic abnormalities have also been identified but none that are uniformly present in infants with this syndrome. Diagnosis can be made with prenatal ultrasound approximately half the time, but the disorder is typically suspected in an infant with copious secretions, suffocation and cyanosis (particularly with breast feeding), and inability to pass an orogastric tube. Prompt recognition is essential with diagnostic testing, including chest radiography and bronchoscopy. The surgical procedure is dictated by the type of atresia and/or fistulization present. Prognosis is dependent on preoperative birth weight, respiratory status, and the rates of morbidity and mortality that may accompany associated anomalies,

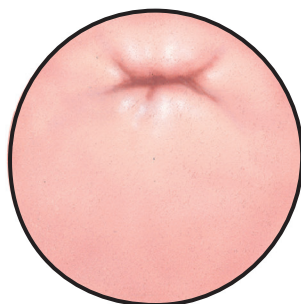
particularly cardiac disorders such as ventricular septal defects and tetralogy of Fallot. Notably, 50% of infants with esophageal atresia have other congenital abnormalities. An acronym used clinically to describe a subset of these infants is VACTERL (vertebral, anal, cardiac, tracheal, esophageal, renal, and limb). The timing of surgery depends on the type of atresia and the respiratory status of the infant. Infants with esophago-tracheal fistulization and/or aspiration need urgent surgery, whereas infants without respiratory compromise may be followed for several months with gastrostomy tube feeding until the esophagus matures and grows and is more amenable to an anastomosis between the proximal and distal ends. One of the great challenges in this surgery is having enough remnant esophagus to accomplish this. Indeed, substitutes may be needed, including stomach or intestinal interposition. Short- and long-term postoperative complications include anastomotic leak and/or stricture and severe gastroesophageal reflux.

ESOPHAGOSCOPY AND ENDOSCOPIC ULTRASOUND

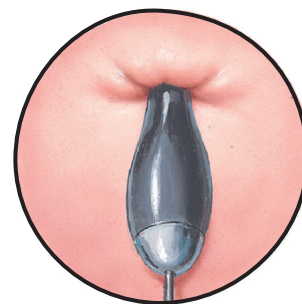
Normal esophagoscopic views



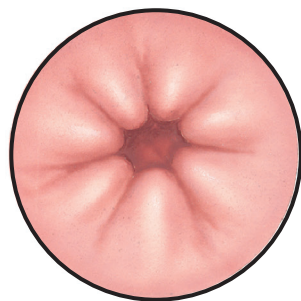
Exposure of piriform fossa



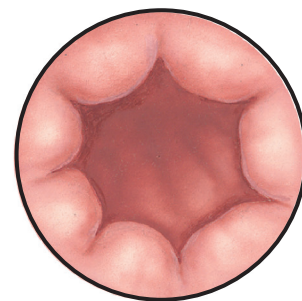
Mouth of esophagus (cricopharynx)



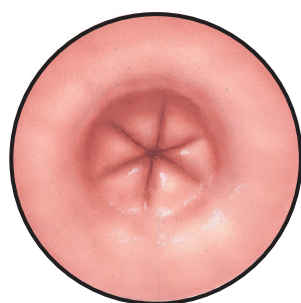
Introduction of lumens-finding bougie to relax cricopharynx



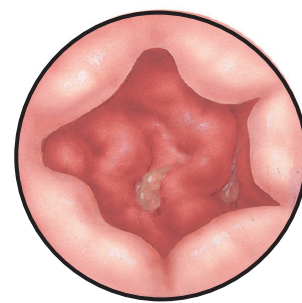
Thoracic esophagus (expiration)



Thoracic esophagus (inspiration)



Inferior esophageal sphincter



Gastroesophageal juncture

ESOPHAGOSCOPY AND
ENDOSCOPIC ULTRASOUND

The ability of being able to introduce a flexible instrument with a charge-coupled device safely into the gastrointestinal tract has revolutionized the practice of gastroenterology. Endoscopic examination of the esophagus shows extensive detail of the mucosal lining, some imaging of abnormalities that lead to intramural or extramural indentation or compression of the lumen, respectively, and esophageal motility abnormalities as estimated by sphincter tone and esophageal diameter. Mucosal abnormalities seen are best characterized as inflammatory or neoplastic. Inflammatory lesions may vary in intensity from mild superficial erythema to frank ulceration with complete destruction of the mucosa. This process may occur distally (e.g., gastroesophageal reflux) or proximally (e.g., lichen planus). The inflammation may also be well localized and discreet (e.g., pill-induced esophagitis), patchy (e.g., candidal esophagitis), or diffuse (e.g., radiation esophagitis or caustic injury). Inflammation may also be seen indirectly as an esophageal stricture representing a sequela of uncontrolled or poorly controlled chronic inflammation. Strictures of the esophagus may appear as bland, tapered narrowings. A stricture may be short or long, sometimes involving the entire esophagus. The diameter of the stricture may be widely patent or pinpoint, depending on the cause, and may occur in any portion of the esophagus. The most common location is the distal esophagus due to the common cause of gastroesophageal reflux. The stricture may have normal-appearing overlying mucosa or frank erythema and ulceration, depending on the activity of the underlying inflammatory process.

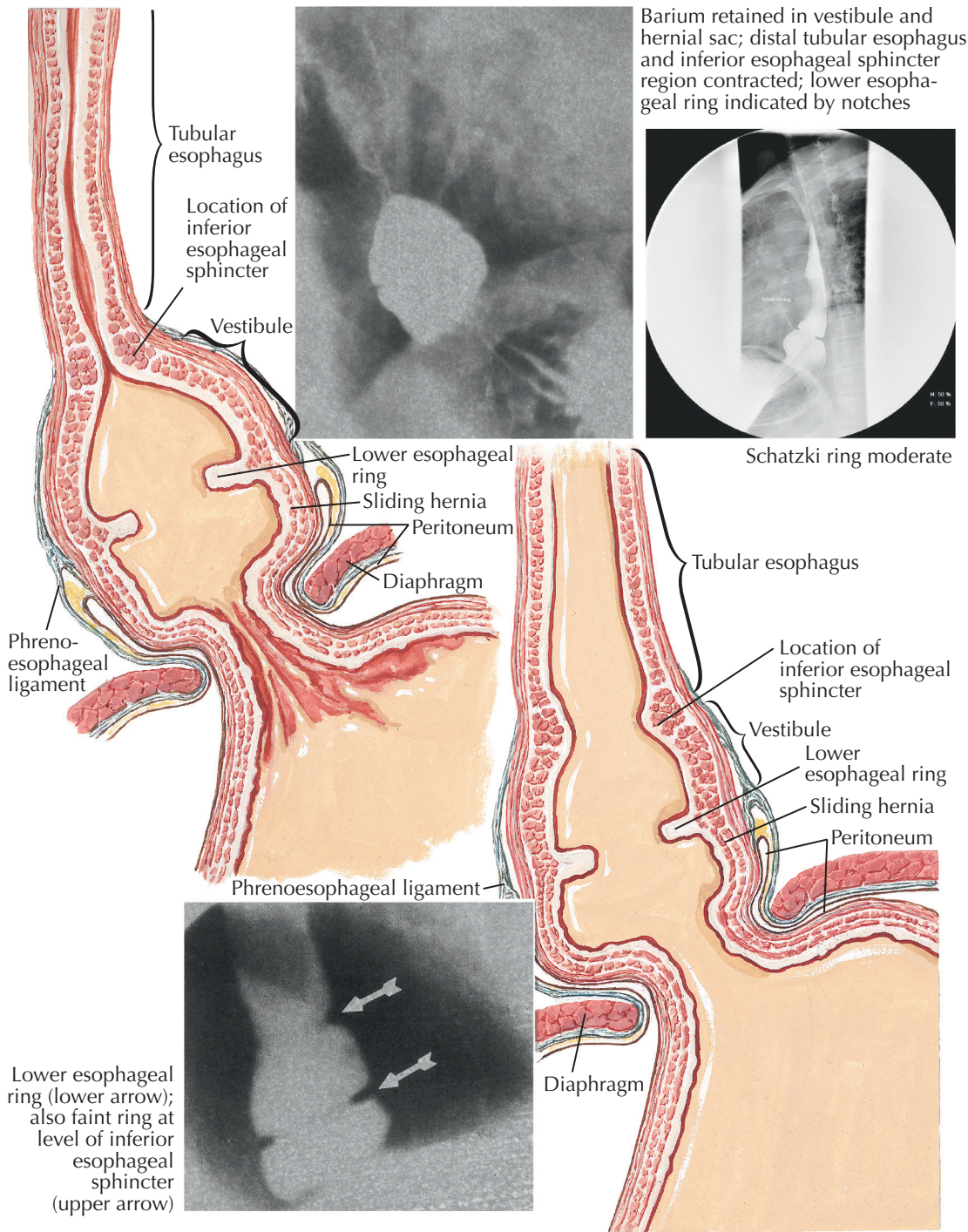
Endoscopic ultrasound relies on standard endoscopic technology but with an ultrasound transducer at the

end of the endoscope. This allows for detailed information on the layers of the esophageal wall and closely apposed structures to the esophagus. Echographically, the esophageal wall is characterized by layers of varying echodensity distinguishing the mucosa, submucosa, and muscularis propria. Newer-generation echoendoscopes may visually further subdivide these layers. This information is essential for numerous esophageal diseases, including assessment of the degree of esophageal wall penetration from a mucosal process such as neoplasia,

identification of a lesion originating in a layer beneath the mucosa, and visualization of periesophageal lymph nodes and other adjacent structures, such as the aorta, heart, and lung. Furthermore, endoscopic ultrasound enhances diagnostic accuracy by allowing for placement of a fine needle into abnormal tissue beneath the mucosa and transmural aspiration of tissue for histologic analysis. Therapeutic applications are also possible by drainage of adjacent cystic structures and abscesses.

F. Netter M.D.

INFERIOR ESOPHAGEAL RING FORMATION



INFERIOR ESOPHAGEAL RING FORMATION

The inferior esophageal ring, eponymously known as a *Schatzki ring*, is a round and regular mucosal web circumferentially indenting the esophageal lumen that forms at the squamocolumnar junction at the gastroesophageal junction. It is a commonly acquired ring typically occurring in middle age and associated with gastroesophageal reflux, though this has never been well proven. More recent data have further demonstrated similar rings in patients with eosinophilic esophagitis, suggesting that the ring may be a response to a chronic inflammatory process other than reflux at the gastroesophageal junction. Further diagnostic difficulties stem from differentiating this ring from an annular peptic stricture. Using strict definitions, the ring contains only mucosa, whereas a stricture is an abnormality of deeper esophageal wall layers with fibrotic changes. The visual appearance may be helpful because a ring seen by radiographic or endoscopic means is a relatively thin membranous structure, in contrast to a stricture,

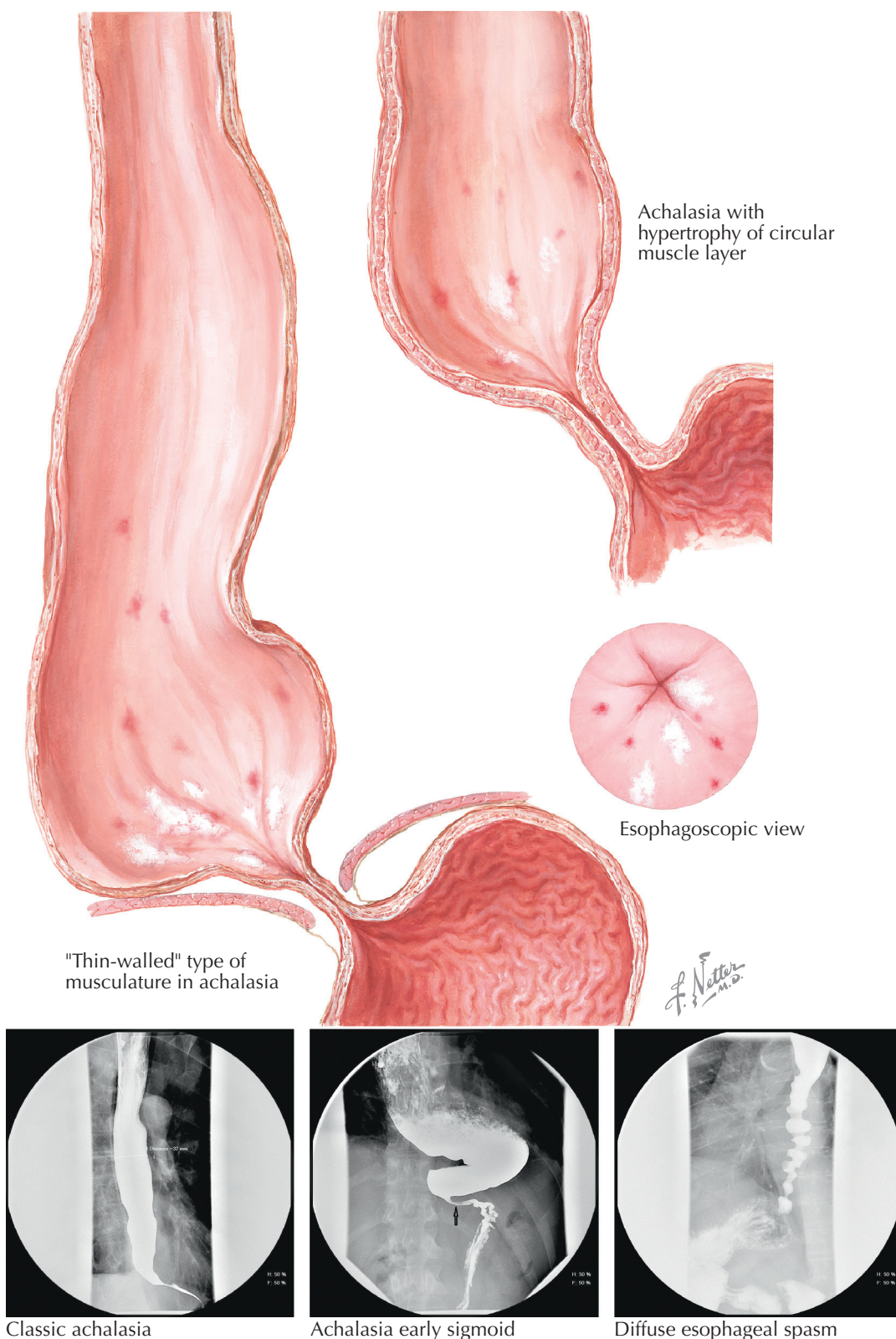
which appears thicker. The cardinal symptoms of an inferior esophageal ring are intermittent dysphagia and/or food impaction with solid food. It is the most common cause of solid-food dysphagia in adults. Because symptoms result from the mechanical process in which a bolus of food that is too large tries to pass through a lumen that is too small, foods that cause symptoms are typically chunky hard solids, such as meats, bread, and raw vegetables. Earlier data suggested that the diameter of the ring dictates the chance of a

food bolus sticking, but other factors, such as types of food, attention to bolus mastication, and use of fluids with the meal, further affect the likelihood of food bolus obstruction. Treatment of an inferior esophageal ring is mechanical disruption, which may be accomplished through biopsy or balloon or Savary dilation. For more recalcitrant rings, endoscopic incision may also be used. Recurrence is common, and pharmacologic antireflux therapy is often used to prevent ring formation, though no data are available to support this recommendation.

ACHALASIA AND DIFFUSE ESOPHAGEAL SPASM

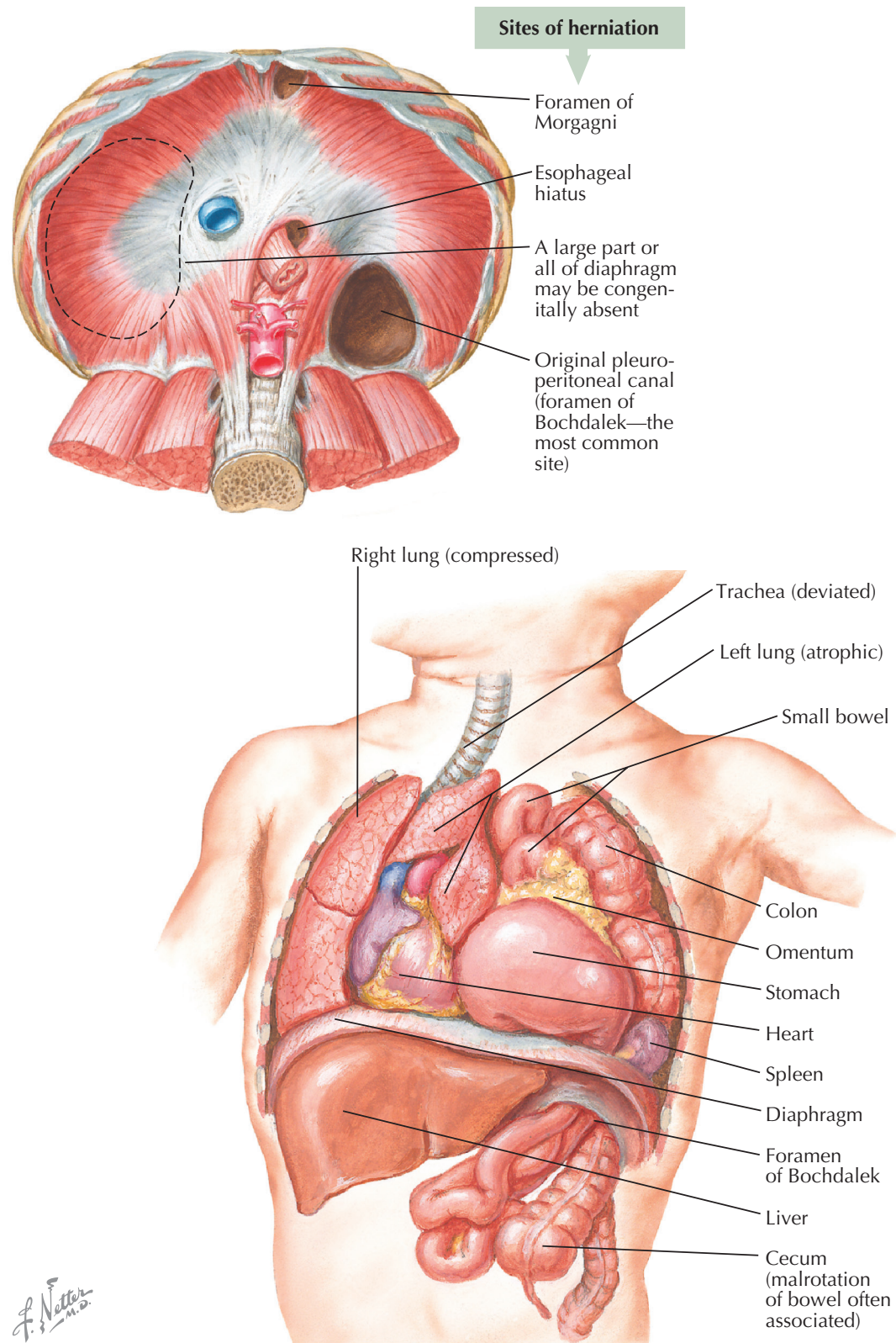
Achalasia is an uncommon disease occurring in 1:10,000 to 1:100,000 people. It results from neurodegeneration of the myenteric plexuses in the esophageal body and lower esophageal sphincter, leading to esophageal aperistalsis and incomplete opening of the lower esophageal sphincter. Whereas the former results from a lack of excitatory input to stimulate peristalsis, the latter occurs from decreased nitric oxide-mediated inhibitory input, leaving the sphincter in a baseline excitatory state with failure to relax in response to deglutition. The initiating event in the pathophysiology remains unclear, but both genetic predisposition and postviral autoimmune mechanisms have been described. Clinically, it is a slow progressive process often masquerading as reflux and typically with a long delay in diagnosis. Without effective treatment, the process continues with progressive dilation of the esophagus, at times, to massive proportions with compression of adjacent structures such as the lung and trachea. Classic symptoms of achalasia are dysphagia to liquids and solids, regurgitation, chest pain, and weight loss. Achalasia patients, however, often learn to adjust their lifestyle to the disease and present with more subtle accommodating symptoms such as slow eating and stereotactic movements with eating, such as sitting up straight or walking during a meal. These maneuvers physiologically increase the longitudinal muscle tone. The diagnosis is made by a combination of compatible symptoms, imaging (radiography and/or endoscopy), and esophageal manometry. Imaging demonstrates a range of findings depending on the severity of the disease. In early stages, a nondilated esophagus with a difficult to pass or incompletely opening lower esophageal sphincter may be seen on endoscopy or radiography. As the disease advances, esophageal dilation is more easily appreciated, often with retained saliva and food present despite prolonged fasting. In the most advanced stages, the esophagus may elongate and dilate similar in appearance to the colon in a process described as “sigmoidization.” Without the ability to alter the underlying neural injury, therapy is aimed at pharmacologic or mechanical disruption of the lower esophageal sphincter to at least allow gravity to facilitate passage of the bolus into the stomach. A simple but relatively short-term treatment is endoscopic injection of botulinum toxin into the lower esophageal sphincter. Pharmacologically, this suppresses cholinergic stimulatory activity and lowers the lower esophageal sphincter pressure. Mechanical therapies include endoscopy dilation with a high-pressure pneumatic balloon to rip sphincter muscle fibers or more precise cutting of the sphincter (myotomy) through a surgical approach. Recently, the latter has been performed completely through endoscopy (peroral endoscopic myotomy) by tunneling through the esophageal submucosa and then incising the inner circular layer of the muscularis propria of the lower esophageal sphincter. Long-term results are not available yet for this novel approach. In severely advanced achalasia with sigmoidization, esophagectomy may be needed. Finally, there is an increased risk of esophageal squamous cell cancer in patients with long-standing end-stage disease.

The pathophysiology of *diffuse esophageal spasm* is likely similar to that of achalasia. The pathophysiology,



however, reflects a more pronounced form of esophageal disinhibition. Specifically, it is manifested by an incompletely relaxing lower esophageal sphincter but also a shorter time interval from the onset of deglutition to lower esophageal sphincter relaxation (decreased distal latency) and hypertensive esophageal contractions. These patients have dysphagia and/or severe episodic chest pain. Radiographically, a “corkscrew” esophagus may be seen. Treatment is similar to that for achalasia, but the response rate of symptoms, particu-

larly chest pain, is not as robust when compared with the response of dysphagia in achalasia. As a result, additional treatment to control the chest pain is often needed. The treatments are aimed at decreasing esophageal muscle pressures (e.g., with anticholinergic or nitric oxide-enhancing medications) or reducing esophageal sensation (e.g., with low-dose tricyclic antidepressants). The number of cases of diffuse esophageal spasm that remain stable or progress to more typical forms of achalasia is variable.



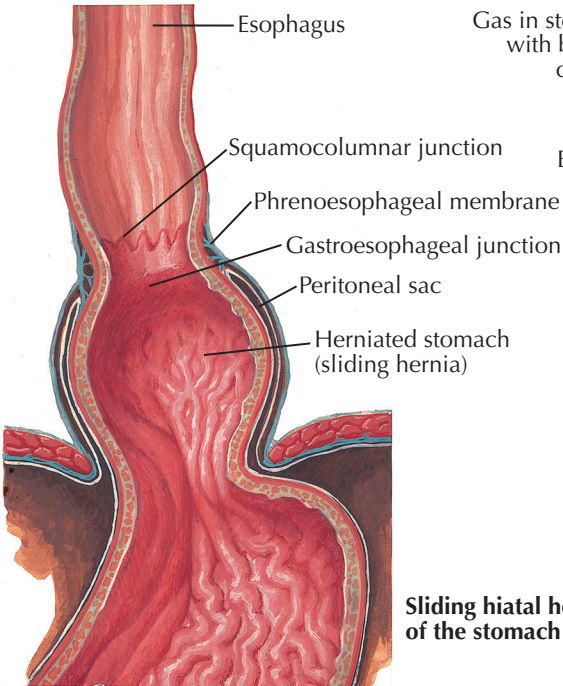
CONGENITAL DIAPHRAGMATIC HERNIA

A congenital hernia of the diaphragm (CDH) develops as a result of a primary developmental diaphragmatic defect that allows proximal herniation of abdominal organs into the thoracic cavity. Approximately 75% of the time, the diaphragmatic defect is posterolateral (*Bochdalek hernia*) and typically on the left side, whereas 25% are anteromedial (*Morgagni hernia*). CDH may

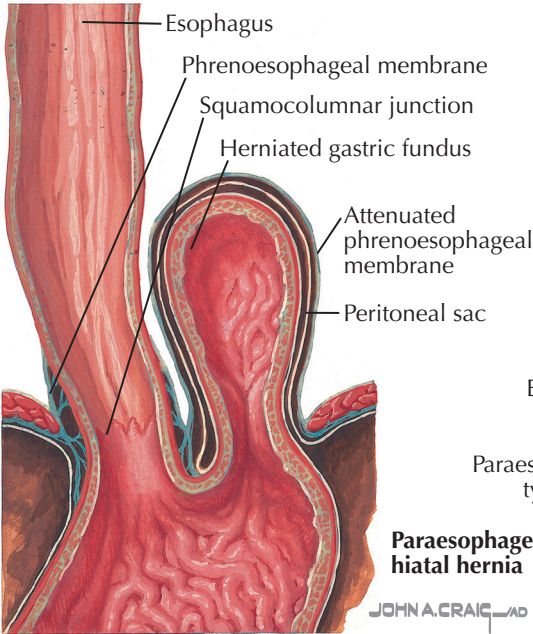
present as respiratory disease due to extrinsic compression of abdominal organs on the developing lungs with pulmonary hypoplasia. Association of CDH with multiple well-defined genetic syndromes, chromosomal abnormalities, or other congenital anomalies strongly suggests a genetic predisposition. Although the stomach is the most common abdominal organ to herniate into the chest, the small and large bowel, liver, spleen, and pancreas may also herniate. Diagnosis is typically made with prenatal ultrasound or is suspected at birth due to

pulmonary compromise. In some patients, the presentation may be much later in life, including adulthood. Symptoms in later life include postprandial upper abdominal and chest pain or acute symptoms of incarceration. Diagnosis is best made through computed tomography of the chest and/or barium studies. The only effective treatment is surgery; visceral organs are reduced into the abdomen, and diaphragmatic defects are either oversewn or patched, depending on the size of the defect.

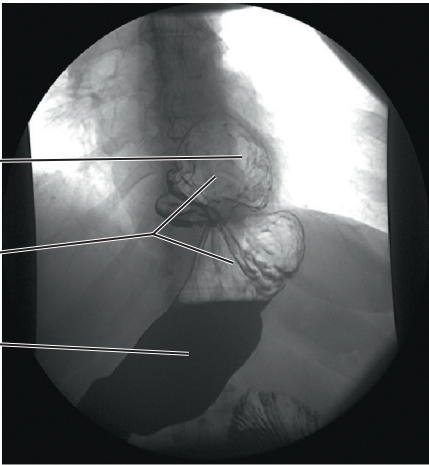
HIATAL HERNIAS



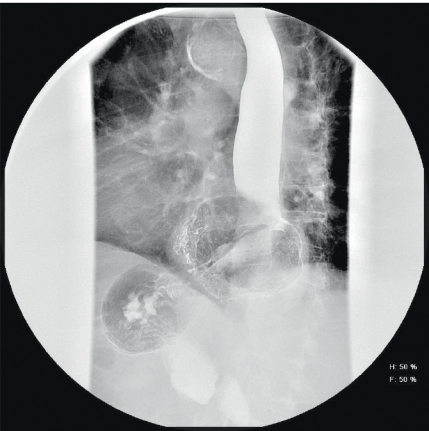
Sliding hiatal hernia of the stomach



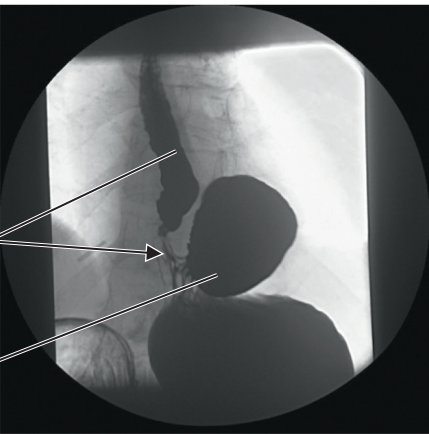
Paraesophageal hiatal hernia



Upper GI fluoroscopy study with double contrast (gas and barium) of a sliding hiatal hernia



Sliding hiatal hernia



Upper GI fluoroscopy study with barium contrast of a paraesophageal hernia

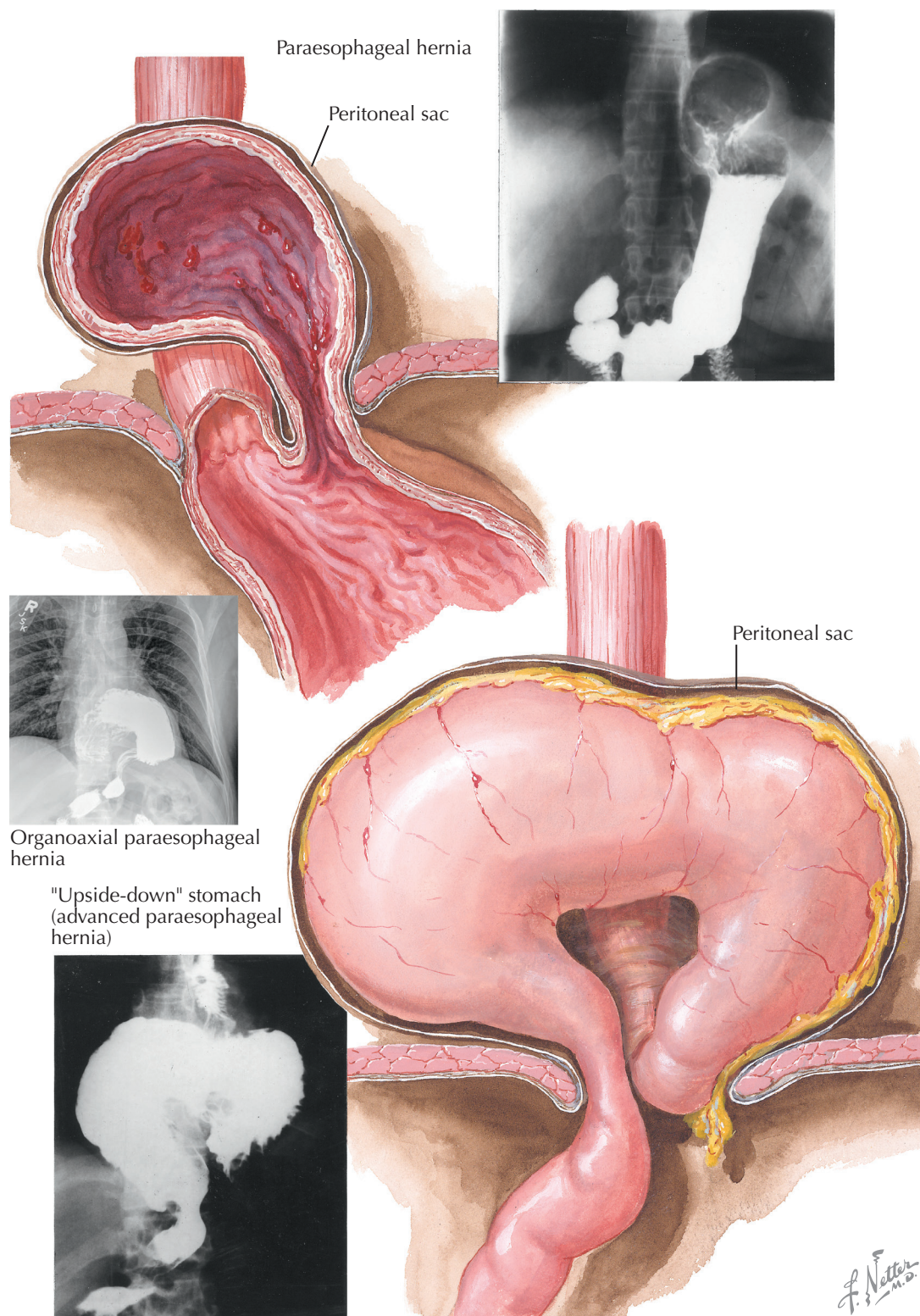
SLIDING AND PARAESOPHAGEAL HERNIA

An acquired hiatal hernia is defined by the proximal movement of a portion of the stomach into the chest through the diaphragmatic hiatus. Within that general definition there are two subsets: a sliding hernia and a paraesophageal hernia. A sliding hiatal hernia occurs as a result of a direct proximal movement of the stomach through the hiatus with the gastroesophageal junction. It is thought to form as a result of laxity of the phrenoesophageal ligament that normally closes the diaphragmatic space around the gastroesophageal junction and anchors the junction in place. It is the most common type of hiatal hernia and is most associated with gastroesophageal reflux. The reason for this is multifactorial and includes (1) loss of the crural diaphragm contribution to lower esophageal sphincter tone, (2) stasis of refluxed content within the hernial sac, and (3) disruption of the acute angle of His, which has a valvelike

function in preventing reflux. With larger crural defects and, hence, diameters of the hernia, these defects are more pronounced and the degree of reflux is greater. As a result, larger hiatal hernias tend to be more associated with complications of gastroesophageal reflux, such as erosive esophagitis, esophageal strictures, and Barrett esophagus. It is also more difficult to control the reflux through lifestyle and pharmacologic interventions; surgical correction such as fundoplication is needed in some patients.

In contrast, in a paraesophageal hernia, the gastroesophageal junction remains fixed in place without proximal migration of the proximal portion of the stomach. Although the herniation is through the phrenoesophageal membrane and hiatal opening, the junction stays in place through its attachment to the periaortic fascia and median arcuate ligament. The herniation may begin with the gastric fundus but in time progresses to include a large portion of the stomach, if not the entire stomach. When a large portion is

PARAESOPHAGEAL HERNIAS

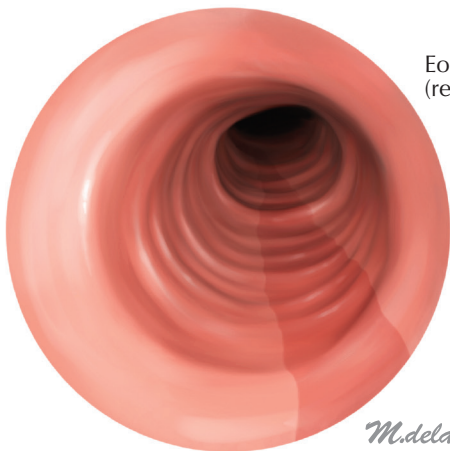


SLIDING AND PARAESOPHAGEAL HERNIA (Continued)

involved, the stomach may flip up through the hiatus by two configurations. The first is in a mesenteroaxial direction, that is, on a dividing line between the proximal and distal stomach. When the entire stomach herniates through the diaphragm into an upside-down position at both the proximal and distal margins of the stomach, this is termed an *organoaxial hernia*. A paraesophageal hernia is not deleterious necessarily because of gastroesophageal reflux but because of the threat of incarceration and strangulation of the stomach in the diaphragmatic hiatus due to vascular compromise of the

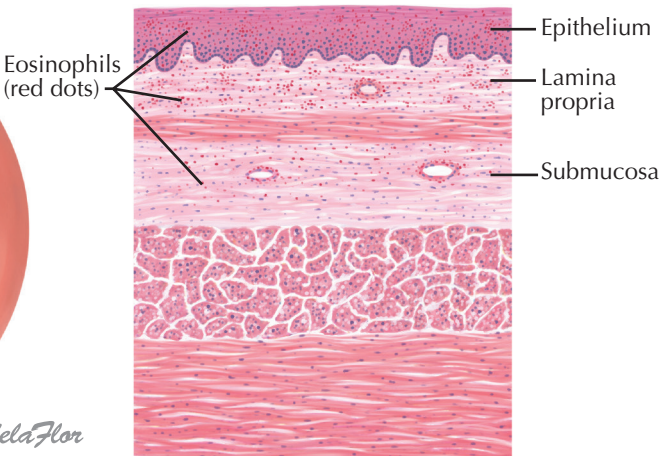
angulated gastric vasculature. Patients may present at first with symptoms of postprandial chest or epigastric pain from partial obstruction and early satiety due to reduction of the size of the gastric pouch. Presentation with incarceration can be catastrophic excruciating chest pain and shock associated with frank gastric infarction and death if not addressed immediately. Surgical correction securing the stomach below the diaphragm and closing of the hiatus is needed for symptomatic patients or a young patient with a large hernia.

With large diaphragmatic defects, organs adjacent to the stomach such as the colon and spleen may also herniate into the chest. Finally, although these types of hiatal hernias are strictly defined, a combination of both a sliding and a paraesophageal hernia is common. These patients may present with both reflux symptoms and symptoms of pouch obstruction. As a result, surgical correction for these patients (if not for most patients with a large hernia of any type) requires both reduction of the hernia and fundoplication.

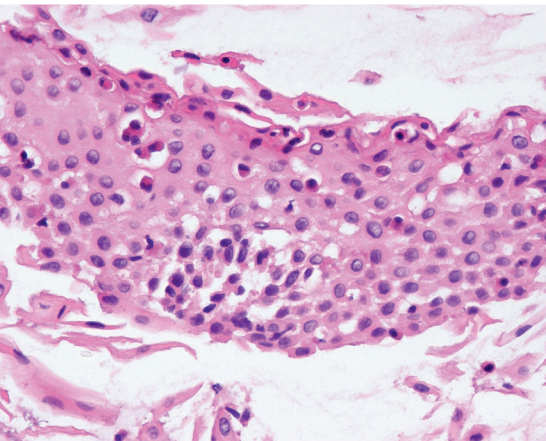


M. de la Flor

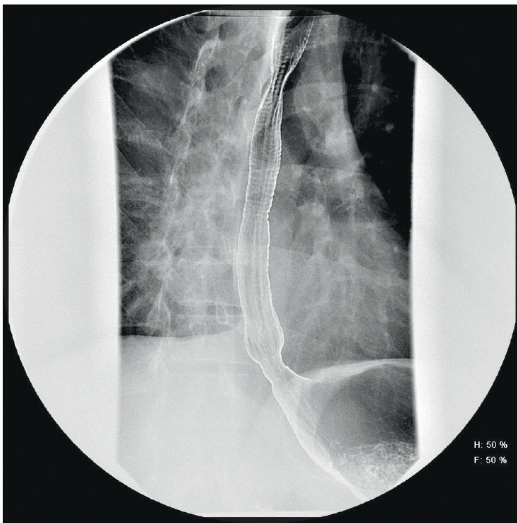
Endoscopic view demonstrates characteristic rings seen in the esophagus with eosinophilic esophagitis



Cross-sectional microscopic view of the esophagus demonstrates the infiltration of all layers of the esophagus with eosinophils. The infiltrate is diagnosed most frequently by endoscopic biopsy so it is seen in the biopsy specimen in the epithelium and lamina propria.



Eosinophilic esophagitis histology



EoE with multiple rings and corrugated appearance

EOSINOPHILIC ESOPHAGITIS

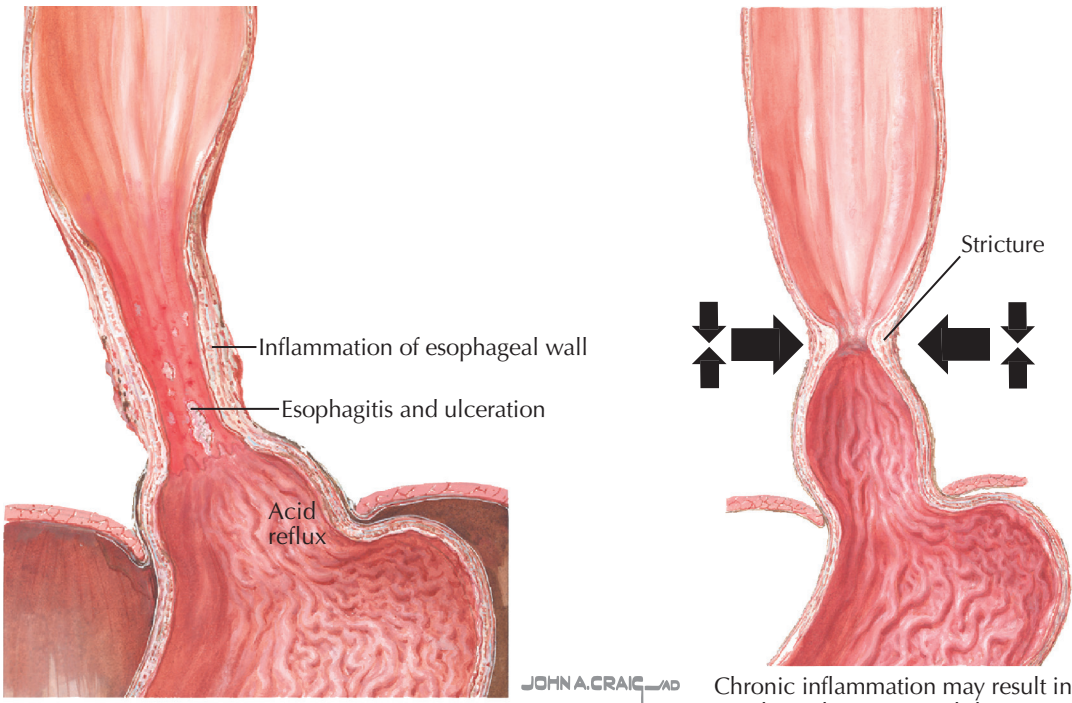
Eosinophilic esophagitis is a newly recognized but common disease defined by the presence of esophageal symptoms in a patient with esophageal mucosal eosinophilia not attributable to gastroesophageal reflux or other causes. It is caused by a combination of an immunoglobulin E response with a TH-2 lymphocyte type of allergic reaction to specific food antigens exposed to the esophageal mucosa with normal eating. This in turn leads to chronic inflammation with dense eosinophilic infiltration. It is more common in men than women and typically affects children, teenagers, and young adults. Both a personal and family history of extraesophageal allergies is common. Children typically have symptoms referable to the inflammatory component of the disease, including failure to thrive, nausea, vomiting, dyspepsia, and heartburn. With time, inflammation leads to fibrosis. As a result, stricture formation is common in this disease, particularly in adults, and dysphagia to solid food becomes the most likely presenting symptom. Strictures may be of variable length, from focal distal strictures to uniform esophageal narrowing (*small-caliber esophagus*). In addition to strictures, endoscopically, the esophagus has several characteristic features,



Eosinophilic esophagitis with linear furrows, rings with white exudates

including white exudates that represent eosinophilic abscesses, linear furrows that are longitudinal mucosal tears, mucosal fragility characterized by easy tearing of the mucosa with minimal trauma, and esophageal rings with a corrugated appearance due to fibrosis. Treatment, particularly in adults, is aimed at both control of the inflammation and dilation of fibrotic strictures. Control of the mucosal eosinophilia may be achieved through medications such as proton pump inhibitors

and topical corticosteroids. The ideal treatment is identification and avoidance of the food antigens that trigger the disease in individual patients. Unfortunately, this is often not practical given the inaccuracy of skin and blood allergy testing to predict causative food antigens and a lack of reliable noninvasive testing to monitor the response to multiple trials of food additions and withdrawals and the multiple foods often identified that need to be avoided.

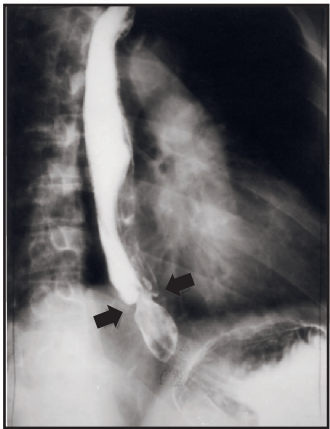


Esophageal reflux may cause peptic esophagitis and lead to cicatrization and stricture formation.

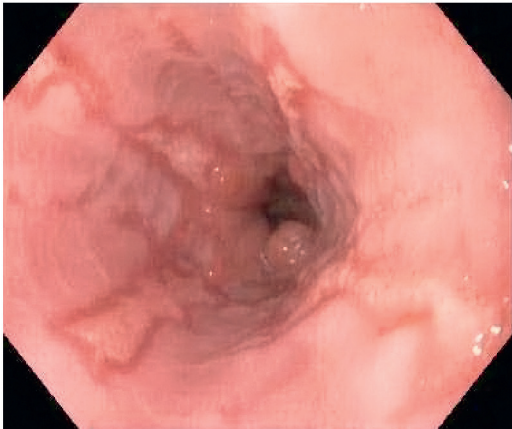
Chronic inflammation may result in esophageal stricture and shortening.

REFLUX ESOPHAGITIS

Gastroesophageal reflux is defined simply as the passage of gastric contents into the esophagus. *Gastroesophageal reflux disease (GERD)* occurs when the content volume is abnormal and is associated with symptoms and/or gross esophageal injury. Within this definition are a multitude of mechanisms and symptoms, some of which are bothersome and some of which can lead to injury and even death. As a result, GERD may be arbitrarily divided into mild and severe forms. In the mild form, symptoms result from reflux but the caustic nature of the refluxant is not of sufficient strength, duration of esophageal exposure, and/or quantity to cause gross esophageal injury. This type of reflux is likely explained by mild dysfunction of the normal mechanisms that prevent reflux from occurring. For example, with the normal transient opening of the lower esophageal sphincter that occurs with activities such as swallowing or belching, there is an excess of refluxed gastric content. This reflux is enough to initiate sensory activation, leading to symptoms such as heartburn or chest pain. Patients with this form of reflux are unlikely to progress to more severe forms and may have their symptoms controlled through medications such as proton pump inhibitors and/or lesser therapies such as lifestyle changes. On the other hand, the more severe form of GERD is one that allows far greater quantities of gastric content, such as acid, bile, and pepsin, into the esophagus to a degree that the normal squamous epithelium and other esophageal defense mechanisms are inadequate to prevent tissue injury. These patients develop erosions, ulceration, strictures, and/or metaplastic changes (*Barrett esophagus*). The mechanisms that contribute to this form of GERD include a hypotensive lower esophageal sphincter, commonly in association with a sliding hiatal hernia, and nocturnal reflux in which the esophagus sits relatively defenseless without gravity or normal swallowing to help with clearance of refluxed caustic gastric contents. When erosive esophagitis occurs, it does so distally, with more



Barium study shows esophageal stricture.



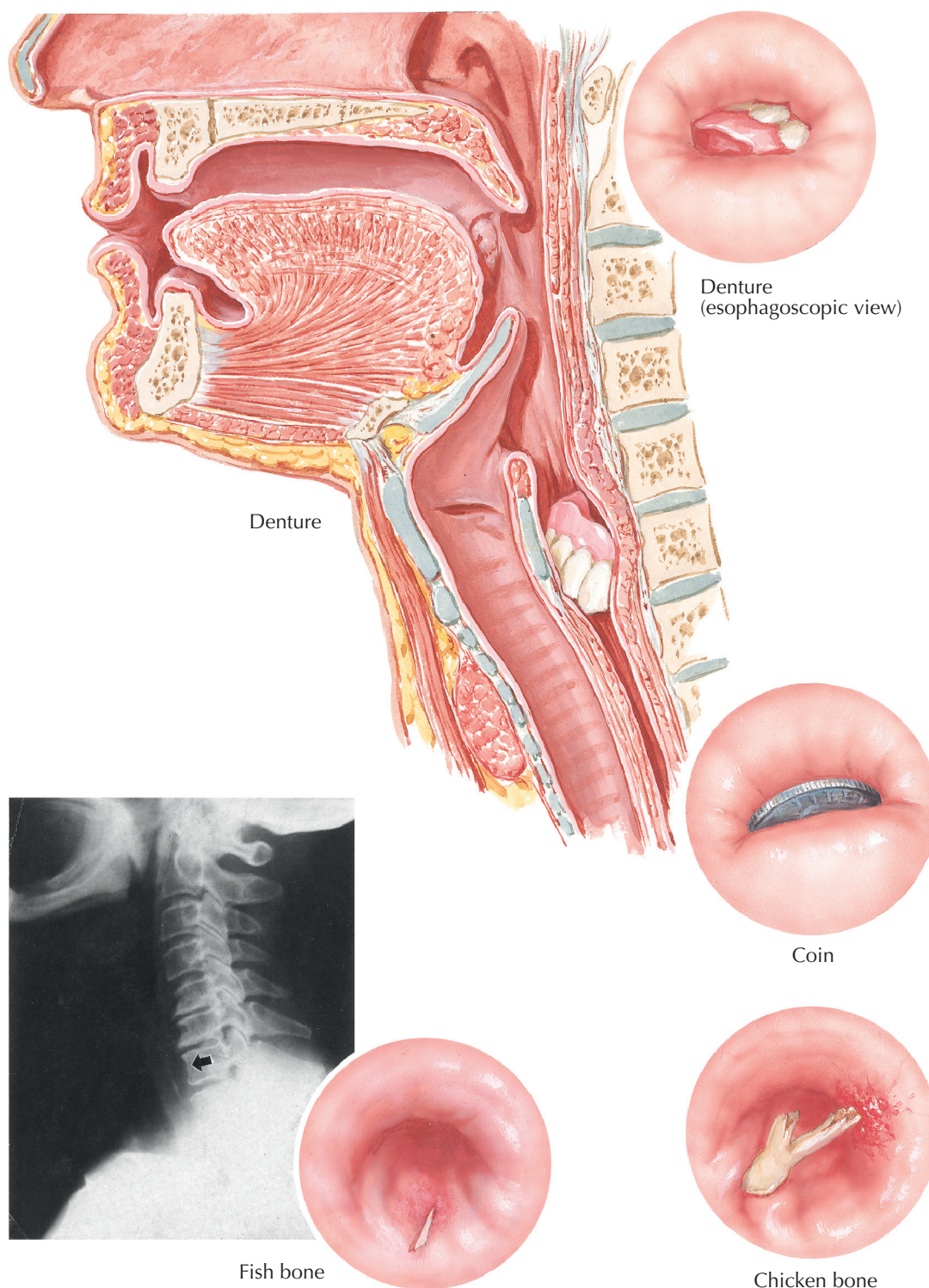
Grade D reflux esophagitis

Los Angeles Classification of Erosive Esophagitis	
Grade A	One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds
Grade B	One (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds
Grade C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involve less than 75% of the circumference
Grade D	One (or more) mucosal break which involves at least 75% of the esophageal circumference

(From Lundell LR, Dent J, Bennett JR, et al: *Endoscopic Assessment of Esophagitis: Clinical and Functional Correlates and Further Validation of the Los Angeles Classification*. *Gut* 1999; 45: 172–180).

extensive and proximal esophageal involvement increasing with greater quantities and proximal movement of esophageal acid and bile exposure. For the purposes of standardizing endoscopic findings in GERD, the Los Angeles Classification of Erosive Esophagitis was developed (see table, above). The importance of this classification lies not only in standardization but with determining treatment. For example, once erosive disease occurs in GERD, particularly grade B and

higher, proton pump inhibitors are needed at the minimum to heal the esophagitis. With high grades of injury, higher doses and sometimes fundoplication may be needed. Also, because the mechanisms that lead to this degree of esophageal injury, such as a large hiatal hernia and incompetent lower esophageal sphincter, are not reversible, these patients need lifelong treatment with proton pump inhibitors or fundoplication to prevent relapse of injury.



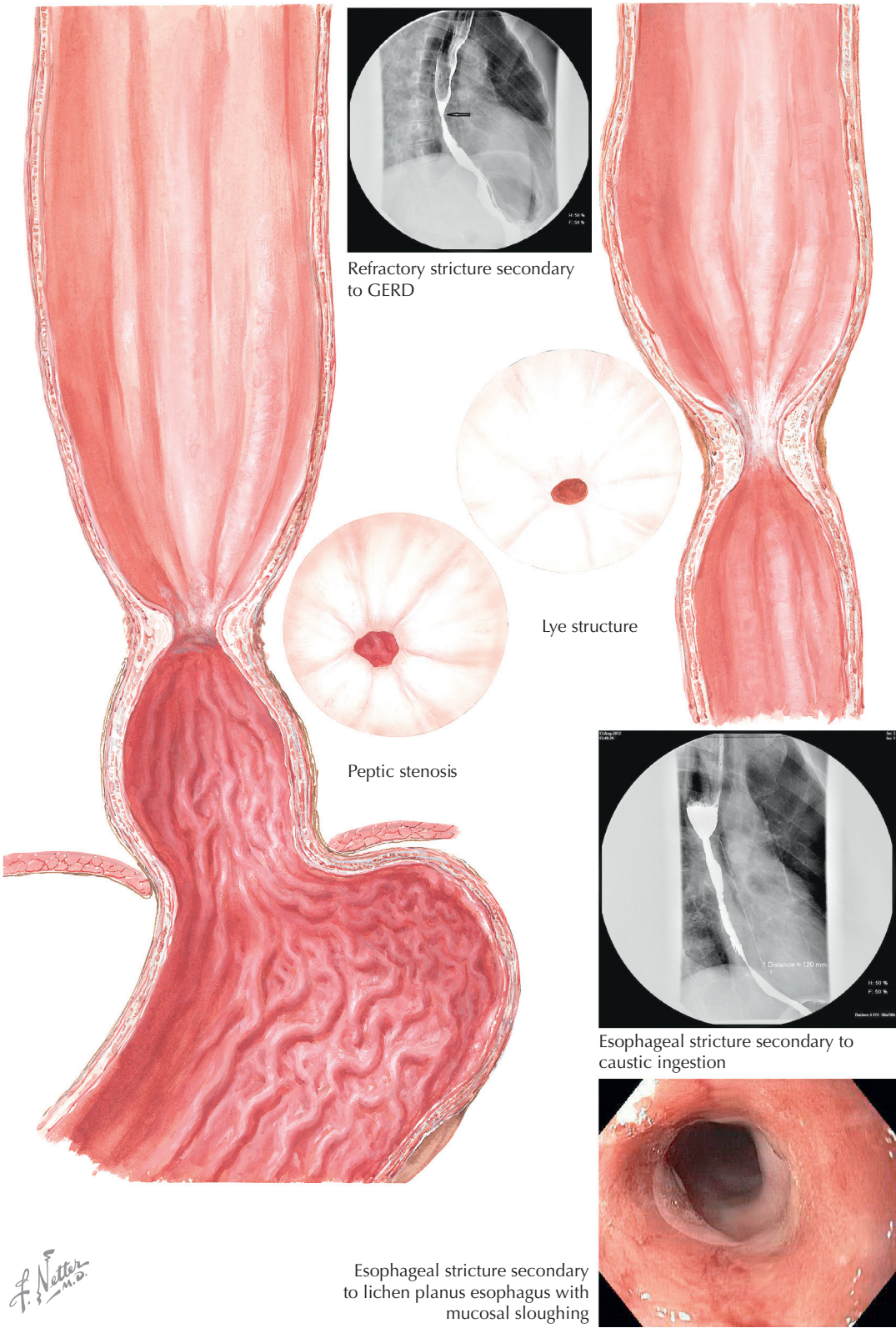
FOREIGN BODIES IN ESOPHAGUS

Classification of esophageal foreign bodies is based on location and type. Location is generally divided into those impactions above and below the cricopharyngeus muscle. Foreign bodies located above the cricopharyngeus are at risk for causing respiratory compromise because of aspiration or tracheal compression. The latter condition is termed *steakhouse syndrome*. There may not be an obvious cause for this impaction other than poor chewing of a large food bolus or a foreign body that has difficulty passing through the upper esophageal sphincter. Nevertheless, areas of narrowing, as with a cricopharyngeal bar, may predispose to this problem. Foreign bodies caught below the cricopharyngeus are termed esophageal. Causes of foreign body impaction in the esophagus may be normal or abnormal areas of narrowing or, less commonly, motility disorders. For example, normal structures that compress the esophagus may include the aortic arch or the right atrium. Abnormal structures that may predispose to impaction of a foreign body include any cause of stricture (e.g., reflux, eosinophilic esophagitis, Schatzki ring, caustic ingestion, or radiation injury), esophageal cancer, or external compression from mediastinal adenopathy or a lung mass. Achalasia may sometimes present with foreign body impaction, particularly if a diverticulum is associated.

The type of foreign body that is impacted in the esophagus is important for management and risk of complications. Food impactions tend to occur with

chunky solids such as meats and breads, which pose the most difficulty passing through a compromised esophageal lumen. As the diameter of the esophageal diameter decreases, the chances of impaction increase. Food impactions may lead to severe complications for two reasons. First, when they completely obstruct, secretions may accumulate proximally in the esophagus and lead to aspiration. Second, with prolonged impaction, pressure necrosis and perforation of the esophageal wall may occur. As a result, urgent removal is indicated. For

true foreign bodies, complications and management depend on the type of object. Objects with pointed or sharp edges, such as pins, bones, or broken glass, pose a high risk of perforation. Other objects pose additional risk to the esophagus by additional mechanisms. For example, button batteries may lead to esophageal wall necrosis from electric shock and from leakage of the caustic alkaline fluid contained in the cell. As in food impactions, immediate removal endoscopically or through other means is urgently needed.



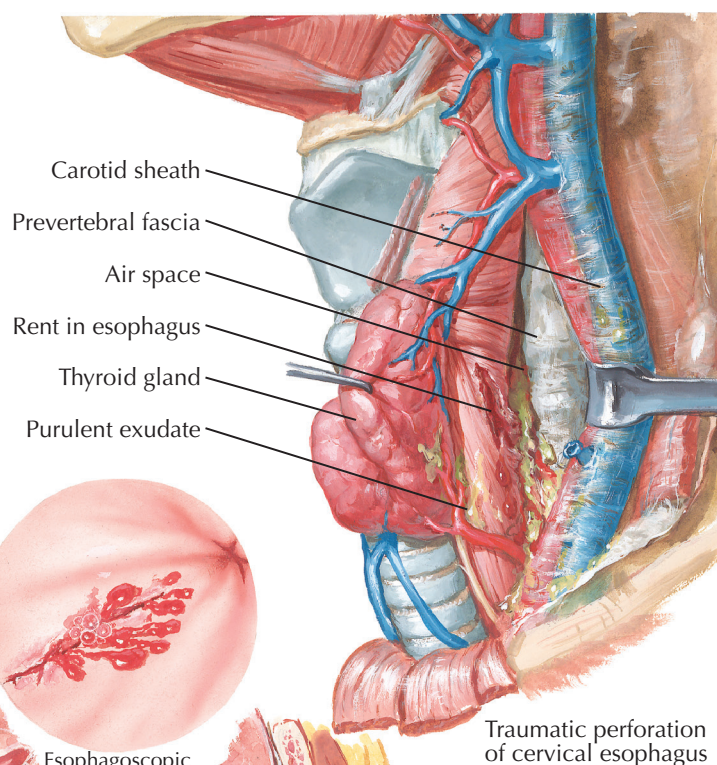
ESOPHAGEAL STRICTURES

An esophageal stricture is characterized by an area of the esophagus in which there is narrowing of the lumen, typically in response to an inflammatory/fibrotic and sometimes a neoplastic process. Strictures may be of variable length, diameter, and location, depending on the underlying cause. Numerous diseases and processes may lead to esophageal stricture formation. The variables that most affect stricture formation are the chronicity and severity of the inflammatory process and the extent of the esophagus involved. For example, acute inflammatory processes such as pill-induced esophagitis tend to lead to self-resolving strictures. In contrast, chronic conditions such as prior radiation exposure lead to long-standing fibrotic strictures in response to chronic unremitting inflammation. Similarly, a disease such as gastroesophageal reflux will most severely affect the distal esophagus given the greater likelihood of acid exposure when compared with the proximal esophagus. In contrast, eosinophilic esophagitis affects the entire esophagus and therefore may cause the entire esophagus to stricture. Other conditions that may involve the

entire esophagus include lichen planus, caustic ingestion, and prolonged nasogastric tube use. Esophageal neoplasia may cause a stricture. For example, primary esophageal cancers such as adenocarcinoma or squamous cell carcinoma may lead to stricture formation through infiltration of the esophageal wall with a combination of inflammatory and neoplastic processes. Indeed, these tumors may present with a linitis plastica pattern similar to that seen in the stomach. Primary esophageal lymphoma may also arise

in the esophageal wall and resemble a long benign stricture. As a result, exclusion of malignancy in patients with esophageal strictures may be challenging when strictures involve the esophageal submucosa and are not readily visible or detected on endoscopic mucosal biopsy. Malignancy may also cause esophageal narrowing without classic stricture formation. For example, submucosal esophageal lesions such as leiomyomas or granular cell tumors may narrow the esophageal lumen but not cause a stricture.

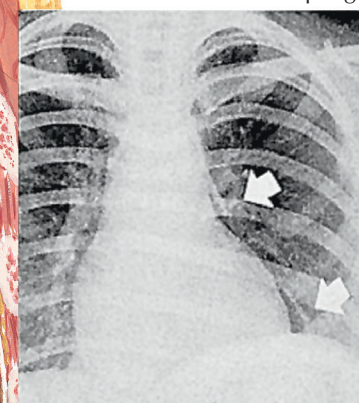
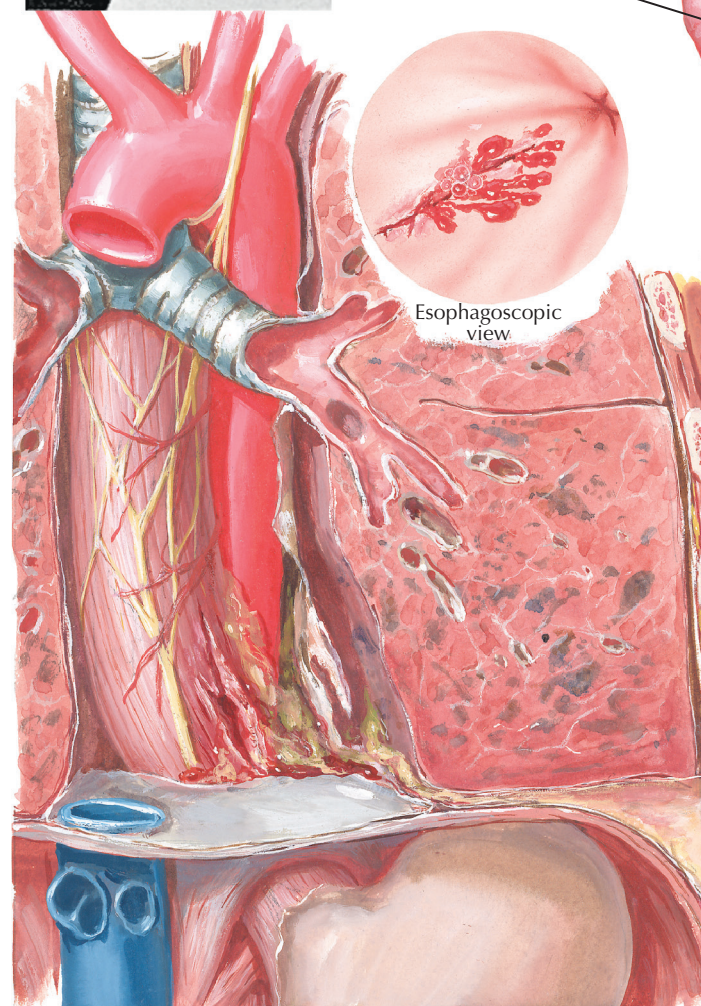
Air in interfascial spaces due to perforation of cervical esophagus



RUPTURE AND PERFORATION OF ESOPHAGUS

Disorders of esophageal rupture and perforation are generally divided into those that present de novo and those that are a result of an iatrogenic complication. Primary esophageal rupture occurs most commonly with prolonged retching (*Boerhaave syndrome*). There are two scenarios in which this is well described. The first is in response to prolonged and forceful retching, particularly in a patient with heavy alcohol use. The second is in a patient with retching secondary to food bolus impaction. In either situation, a large tear of the distal esophagus occurs, with free rupture into the pleural space, often with fluid translocation. Boerhaave syndrome is associated with high rates of morbidity and mortality due to the severity of an associated underlying illness such as alcoholism and the contamination of the pleural and/or mediastinal cavity from food and bacteria, as is typical of food impaction. The diagnosis is suspected in a patient with prolonged retching who presents with severe chest and epigastric pain, fever, crepitus, and sepsis. Diagnosis is suspected on chest radiography with mediastinal and subcutaneous air and confirmed with an esophageal contrast study using Gastrografin. Whereas treatment almost always included surgery in the past, an alternative has become esophageal stenting, drainage of pleural cavity collections, and giving broad-spectrum antibiotics as early as possible.

Perforation of the esophagus may also occur as a complication of specific factors. One of the most common causes is swallowing a foreign substance or body. For example, accidental or intentional caustic ingestion of a strong acid or alkaline solution may lead to esophageal necrosis and perforation, with high mortality rates. Sharp foreign bodies such as toothpicks or pins may also lead to esophageal perforation. These objects often perforate physiologic areas of esophageal lumen narrowing, such as the aortic arch or lower esophageal sphincter. Perforation may also occur in the setting of a prolonged episode of food impaction, even without retching. In these patients, continued disten-



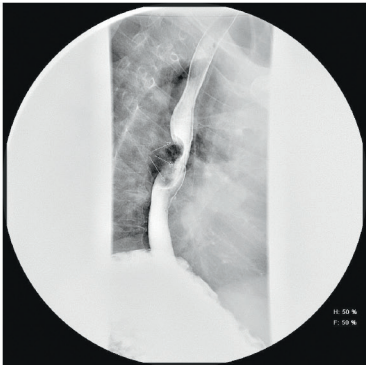
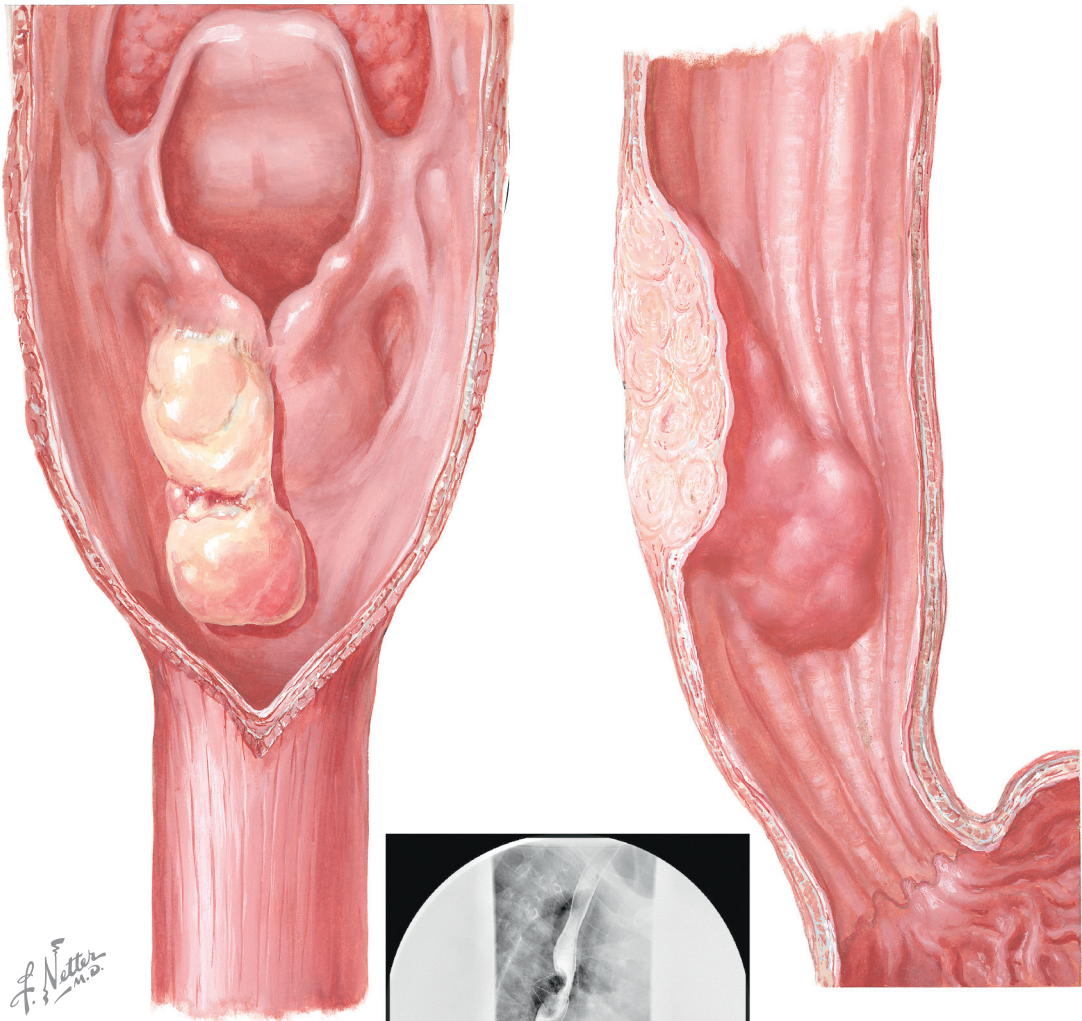
Air in mediastinum due to spontaneous rupture of lower esophagus

Spontaneous rupture of lower esophagus

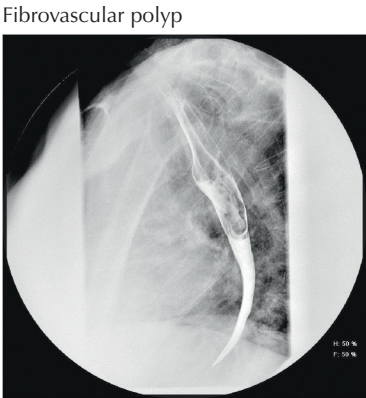
tion of the esophageal wall leads to pressure necrosis and perforation. Finally, esophageal perforation may occur through external trauma, such as a knife or gunshot wound, or even blunt trauma with perforation of the esophagus on a spinal process. As in all esophageal perforations, rapid diagnosis and treatment are essential.

Most perforations of the esophagus occur as a result of endoesophageal iatrogenic instrumentation. Of these, gastrointestinal endoscopy is the most common.

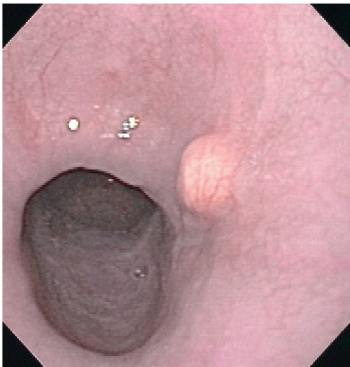
Although routine diagnostic esophagoscopy rarely leads to perforation, adjunct procedures such as dilation of strictures and sphincters, removal of a foreign body, or mucosal resection or ablation pose an increased risk for full penetration of the esophageal wall. Cardiac devices such as transesophageal echocardiography or cardiac ablation techniques may also lead to esophageal rupture. Intubating the esophagus with a rigid tube such as a rigid endoscope or overtube also poses an increased risk for perforation.



Esophagus leiomyoma



Fibrovascular polyp



Granular cell tumor

BENIGN TUMORS OF ESOPHAGUS

The most common benign tumor of the esophagus is a *granular cell tumor (GCT)*. GCTs are stromal lesions originating from the Schwann cells of the submucosal neuronal plexus and are S100 positive on histologic staining. About 5% to 11% of GCTs occur in the gastrointestinal tract, of which one third occur in the esophagus. These tumors are usually detected incidentally during endoscopy with a submucosal appearance and characteristic overlying yellow or white hue. They may occur anywhere in the esophagus and may be multiple. They appear to be of low malignant potential, though endoscopic mucosal resection can be safely performed. *Leiomyomas* are uncommon benign tumors of the esophagus derived from smooth muscle cells. They may be found incidentally during endoscopy or present with dysphagia, with sizes up to 10 cm reported. They are most commonly found in middle-aged men in the midesophagus, though they may be found in all esophageal locations. Malignant transformation is rare, but there is some support for early removal through thoracic

coscopic enucleation to prevent progression to a size large enough to cause symptoms and require more extensive surgical resection. *Gastrointestinal stromal tumors of the esophagus* are similar mesenchymal tumors but are even rarer in the esophagus. They derive from interstitial cells of Cajal and are c-kit positive on histologic staining. The treatment approach is similar to that for leiomyomas. *Fibrovascular polyps* are rare benign esophageal tumors occurring typically in the proximal esophagus. They are

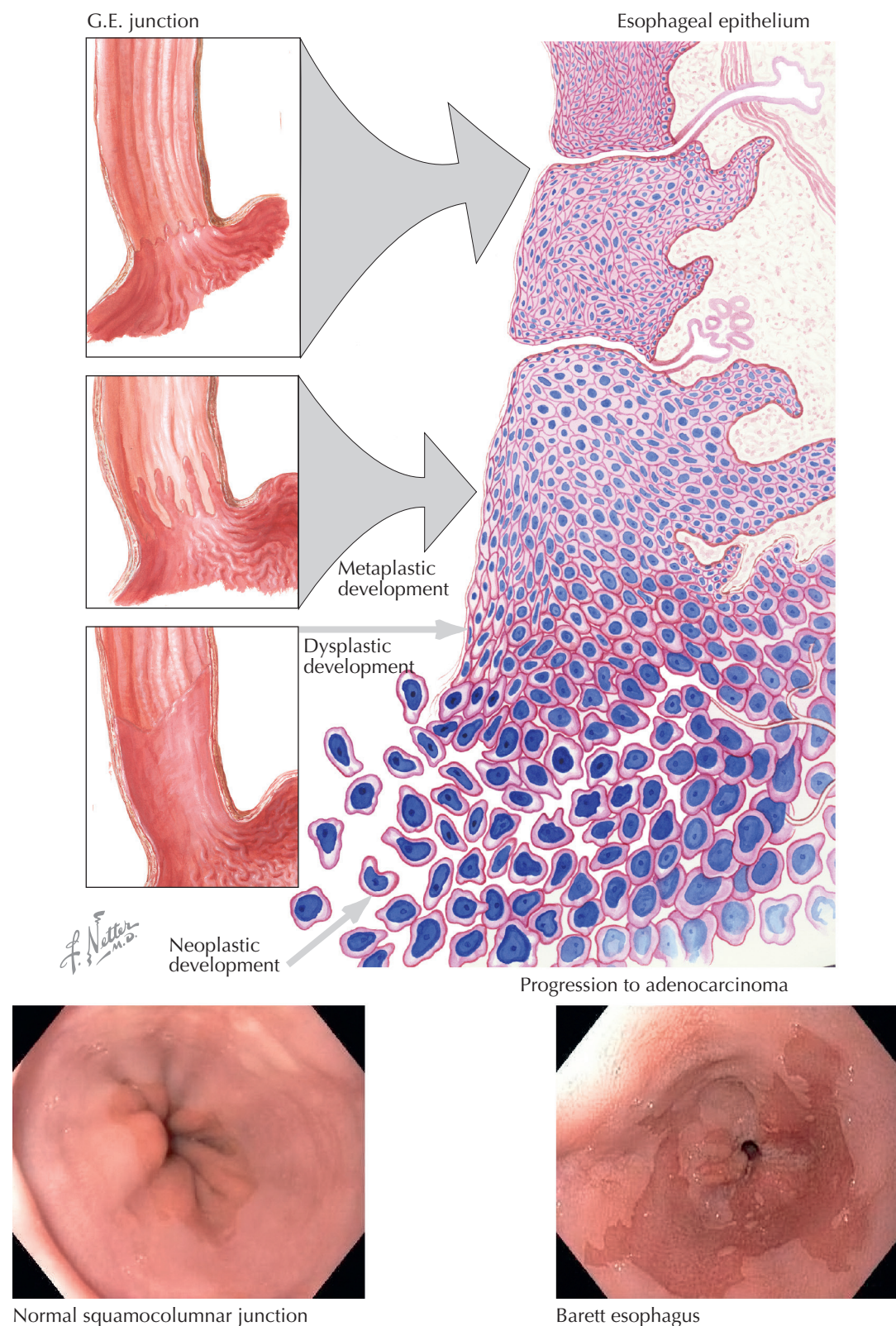
composed of a variable mixture of fibrous tissue, fat, and vascular elements. They may reach a large size and typically present with dysphagia once symptomatic. Classically, patients may note regurgitation of a large mass that snaps back with swallowing. As a result, there is also a risk of asphyxiation. Treatment is surgical resection that may be performed intraluminally in many patients. *Inflammatory esophageal polyps* are also likely reactive growths and are approached in a manner similar to that for fibrovascular polyps.

BARRETT ESOPHAGUS

The current definition of Barrett esophagus is very different from the original definition proposed by Dr. Norman Barrett. Barrett esophagus is presently defined by the presence of metaplastic tissue in the distal esophagus resulting from chronic gastroesophageal reflux. The etiology of Barrett esophagus is primarily gastroesophageal reflux, but other important risk factors are involved. For example, Barrett esophagus occurs predominantly in white men. This may in part reflect a genetic predisposition but also an increased incidence of central obesity in white men. Cigarette smoking is also a likely cofactor, and *Helicobacter pylori* infection is protective.

Defining the presence of Barrett esophagus is unfortunately easier said than done for two reasons: (1) There is no clear definition of the endoscopic appearance of a normal squamocolumnar junction and, therefore, of what defines a clear demarcation between the esophagus and the proximal stomach. This is problematic because nearly 20% of normal adults have metaplastic tissue in the gastric cardia adjoining the distal esophagus, leading to confusion when a putative esophageal biopsy is taken errantly from the gastric side. As a result, many patients are mislabeled as having Barrett esophagus from biopsies taken incidentally from the gastric cardia. (2) It is primarily the intestinalized metaplastic tissue that carries the premalignant potential of Barrett esophagus. On the other hand, esophageal metaplastic epithelium is commonly admixed with both cardiac and intestinal metaplasia, making the finite sampling of endoscopic biopsies limited in confirming the presence of extant intestinal metaplasia. As a result, the British guidelines include both gastric and intestinalized epithelium in the definition of Barrett esophagus. Diagnostic criteria thus vary amongst gastrointestinal societies.

Endoscopically, the distal esophagus is examined for the appearance of a salmon-colored mucosa, different from the normal pink-white squamous mucosa, encroaching proximally at the normal squamocolumnar junction. For the reason cited above, however, arbitrary minimum lengths of this encroachment may be defined from 1 mm to 2 cm above the gastroesophageal junction. Patients are somewhat arbitrarily divided into those with long-segment disease (> 3 cm) or short-segment disease (< 3 cm). The Prague classification



more precisely categorizes the extent of the circumferential and maximal lengths of grossly metaplastic epithelium.

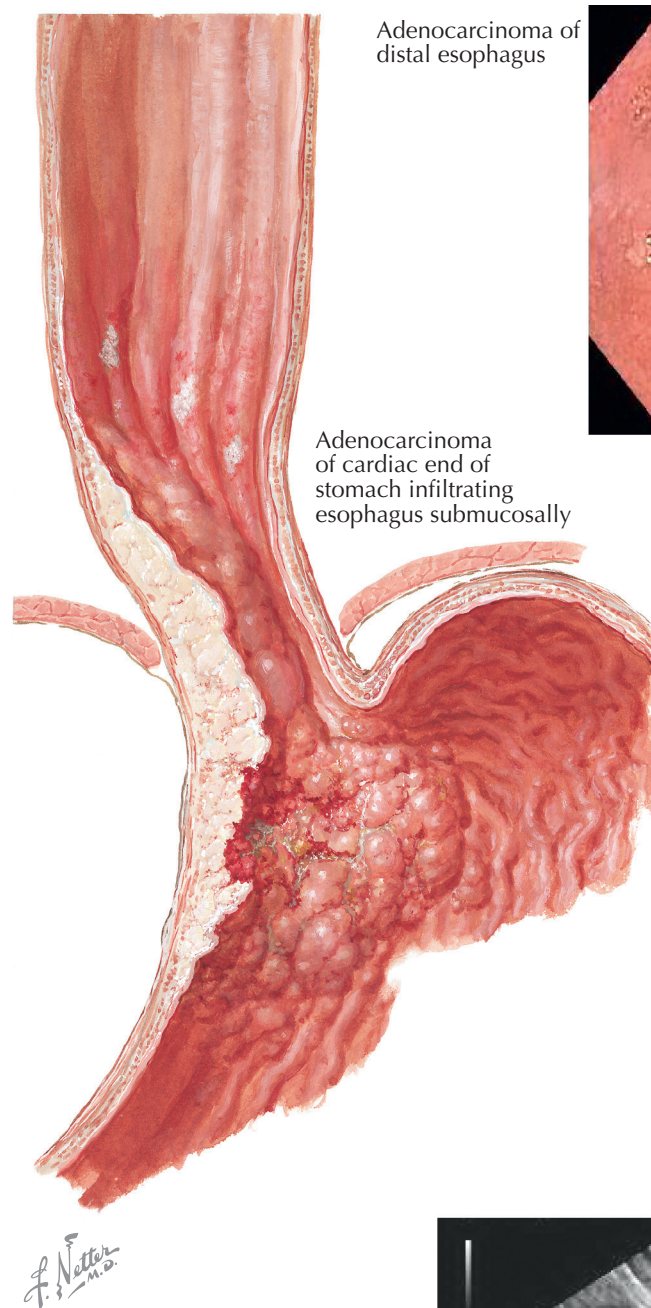
There are two concerns with Barrett esophagus. The first is that it represents a severe form of gastroesophageal reflux with an associated risk of erosive esophagitis and stricture formation. The second is that it has premalignant potential given the cellular instability of metaplasia. Although the estimates of developing adenocarcinoma are low (0.2% to 0.4% per year), they are

derived from surveillance programs that miss most prevalent forms of adenocarcinoma. Treatment consists of controlling the reflux pharmacologically or surgically and asking the patient to participate in endoscopic surveillance programs for potential detection of dysplasia and cancer. For patients who develop dysplasia, there is also the evolving option of radiofrequency ablation of the Barrett mucosa and/or endoscopic mucosal resection to avoid development of cancer and the need for esophagectomy.

ADENOCARCINOMA OF ESOPHAGUS

Adenocarcinoma of the esophagus generally, if not consistently, arises from Barrett esophagus, that is, metaplastic intestinal epithelium in the esophagus. It therefore has the same risk factors as Barrett esophagus, such as chronic gastroesophageal reflux, white race, male gender, central obesity, and cigarette smoking. It may arise anywhere within the region of the Barrett esophagus; its origin thereby determines its potential location within the esophagus. In other words, in patients with short-segment Barrett esophagus, cancer will develop in the distal esophagus, whereas in patients with long-segment Barrett esophagus, both the distal and middle thirds are susceptible to neoplastic transformation. Adenocarcinoma rarely develops in the proximal esophagus. The most common presenting symptom is dysphagia due to narrowing of the lumen either by the mass lesion itself or as a malignant stricture. Some patients may have iron deficiency anemia due to occult bleeding from tumor areas of friability and ulceration. Weight loss and early satiety are also common, the latter due to infiltration and fixation of the proximal stomach with loss of gastric accommodation function. Notably, these patients do not usually have reflux symptoms; if they do, symptoms are mild enough or far enough in the past that patients have not undergone screening endoscopy for Barrett esophagus. This may explain why less than 10% of patients found to develop esophageal adenocarcinoma are enrolled in a Barrett esophagus surveillance program.

There are several staging systems for adenocarcinoma of the esophagus. The TNM system is one of the most commonly used. The T stage defines the depth of



Adenocarcinoma of distal esophagus

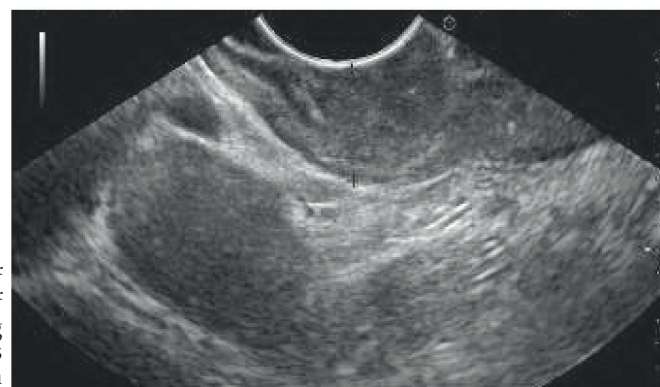
Adenocarcinoma of cardiac end of stomach infiltrating esophagus submucosally



PET scan demonstrating imaging of distal esophageal adenocarcinoma

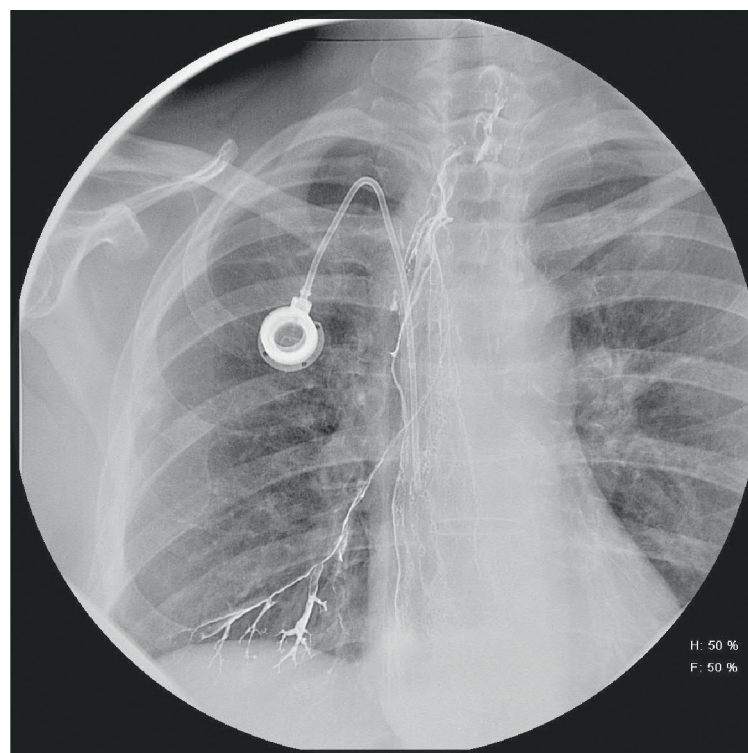
J. Netter M.D.

Endoscopic ultrasound of adenocarcinoma of esophagus demonstrating penetration to muscularis propria

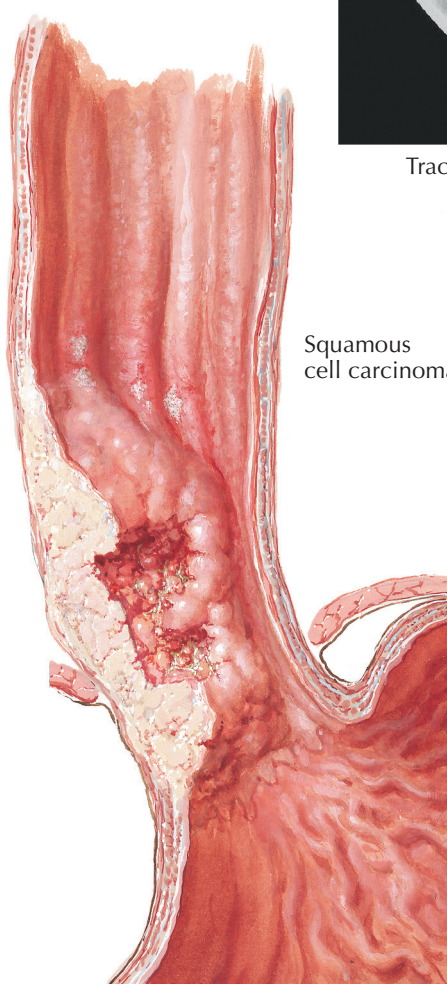


penetration into the esophageal wall: T1 defines tumor confined to the mucosa, T2 up to the muscularis propria, T3 through the muscularis propria, and T4 extending outside the esophagus. The N stage defines the degree of lymph node involvement: N1 is defined by one to three nodes, N2 by three to six nodes, and N3 by more than six nodes. The M stage denotes whether metastatic disease is present. There are further

subdivisions within some of these gradations; for example, T1 may be divided into specific levels within the mucosa and submucosa. This staging system is important not only for determining the prognosis and chance of extraesophageal spread but in determining the appropriate treatment, particularly with regard to endoscopic versus surgical resection and the need for adjuvant chemoradiation therapy.



Tracheoesophageal fistula secondary to squamous cell carcinoma



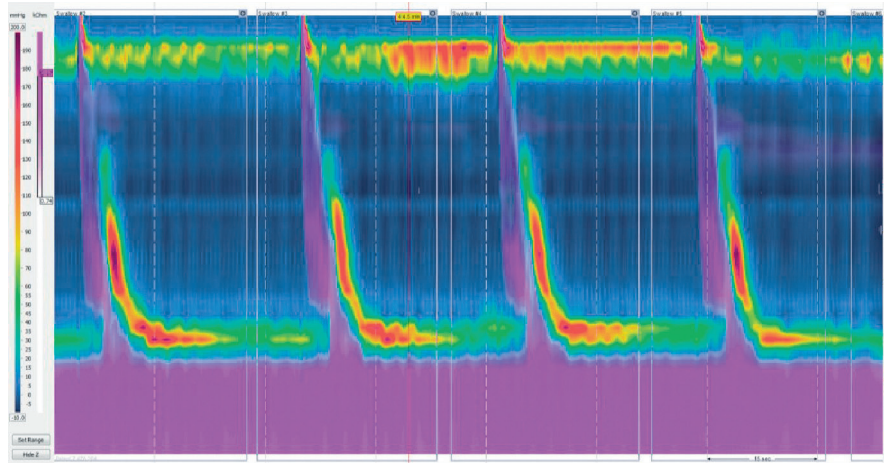
Squamous cell carcinoma

SQUAMOUS CELL CARCINOMA OF ESOPHAGUS

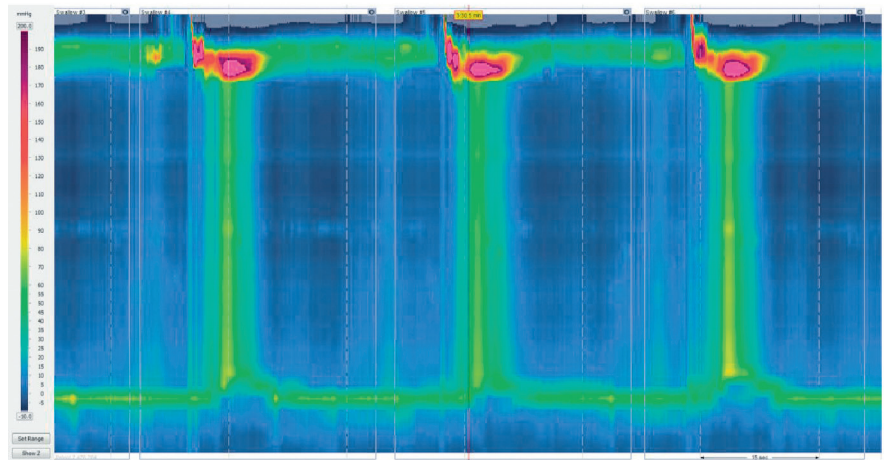
Whereas squamous cell carcinoma was the primary esophageal malignancy for centuries in Western countries, it has become relatively uncommon when compared with adenocarcinoma in the Western world. This is likely due not only to increasing risk factors for adenocarcinoma (e.g., obesity) but to a decrease in risk factors for squamous cell carcinoma (e.g., smoking and heavy alcohol use). Nevertheless, worldwide it is still the most common type of esophageal cancer, particularly in China and Africa. In addition to smoking and alcohol, other risk factors such as infection with human

papillomavirus or Epstein-Barr virus and other environmental and dietary exposures have been proposed. Additionally, a history of squamous cell carcinoma of the head and neck increases the chances of subsequent esophageal cancer. Unlike adenocarcinoma, there is no clear underlying condition that allows targeting of specific populations for screening and surveillance other than certain geographic locations and lifestyle factors as discussed. It is more common in men than women. The most common presenting symptoms are dysphagia

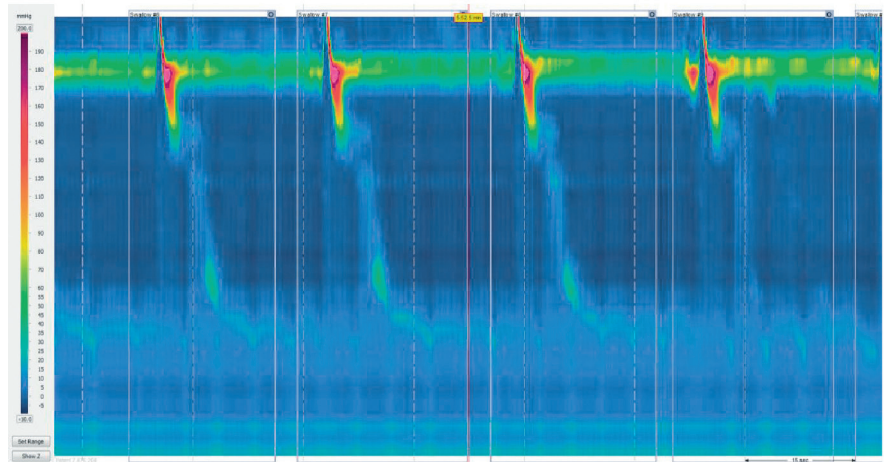
and weight loss. Endoscopy is the most reliable means of diagnosis; a mass lesion is most commonly found in the proximal esophagus. Given the proximal location of squamous cell esophageal cancer, catastrophic complications, including fistulae to the respiratory tract or aorta, may develop. Staging is defined in a manner similar to that for adenocarcinoma, but treatment involves less surgery given the complexities of esophageal resection when the tumor is high in the proximal esophagus adjacent to respiratory structures.



Normal esophageal manometry and impedance study



High-resolution manometry of achalasia showing hypertensive LES with inadequate relaxation and isobaric panesophageal pressurizations



Scleroderma esophagus with low pressures in distal two thirds of esophagus and LES

**DIAGNOSTIC AIDS IN
ESOPHAGEAL AND
GASTRIC DISORDERS**

**HIGH-RESOLUTION MANOMETRY AND
IMPEDANCE MEASUREMENT**

Stationary esophageal manometry as a measure of esophageal motility has been in use for over 50 years.

Although it has become essential for disorders such as achalasia, its accuracy and reliability have been questioned for several reasons: (1) Only a small number of unidirectional pressure transducers can be used for recording. (2) Due to a relatively short catheter length, areas of the esophagus must be analyzed during different time periods by pulling the manometric catheter through the various esophageal segments. (3) There is only a measure of pressure and not of corresponding

bolus transit. With the advent of high-resolution impedance manometry, these limitations have been overcome. This results from the design of a catheter that can measure pressures with 36 transducers, including circumferential transducers. This catheter also spans the length of the esophagus for simultaneous measurement of both the upper and lower esophageal sphincters and the esophageal body that allows the study of simultaneous esophageal parameters. Complete esophageal

DIAGNOSTIC AIDS IN ESOPHAGEAL AND GASTRIC DISORDERS (Continued)

motor function may be measured in response to stimuli, such as swallowing, with far greater accuracy and ease.

Bolus transit can be measured, also simultaneously, by transducers that measure impedance. This functions on the principle of Ohm's law that Voltage (V) = Current (I)/Resistance (R). Within the catheter, voltage is generated between adjacent electrodes and the generated current is a function of the resistance or impedance to current flow. When an electrolyte-rich fluid passes over the electrodes, the current is easily conducted due to the low resistance and high conductivity of this fluid, and therefore measured impedance to current will be low. If one measures impedance over a series of electrodes that span the transesophageal catheter, one can measure the direction and velocity of the movement of an administered bolus. Thus, giving a water swallow as part of the standard protocol for performing high-resolution manometry will assess not only the esophageal body and sphincter pressure dynamics but also the water flow that occurs with these pressure changes. Measurement of impedance will distinguish different types of substance in the esophagus by their conductive properties.

A catheter that independently measures esophageal impedance may also be used for diagnosis in disorders such as gastroesophageal reflux. When such a catheter is made ambulatory and is combined with pH recording, a continual measurement of bolus movement and pH can be made over relatively long periods of time out of the hospital. An ambulatory pH/impedance catheter can measure all fluid that refluxes into the esophagus in addition to the degree of acidity. This test currently serves as the gold standard for diagnosis of either acid or nonacid gastroesophageal reflux. This test may be performed with all therapies suspended to establish a baseline degree of gastroesophageal reflux, or with therapy continuing to determine if persisting symptoms are due to inadequate reflux therapy or another cause.

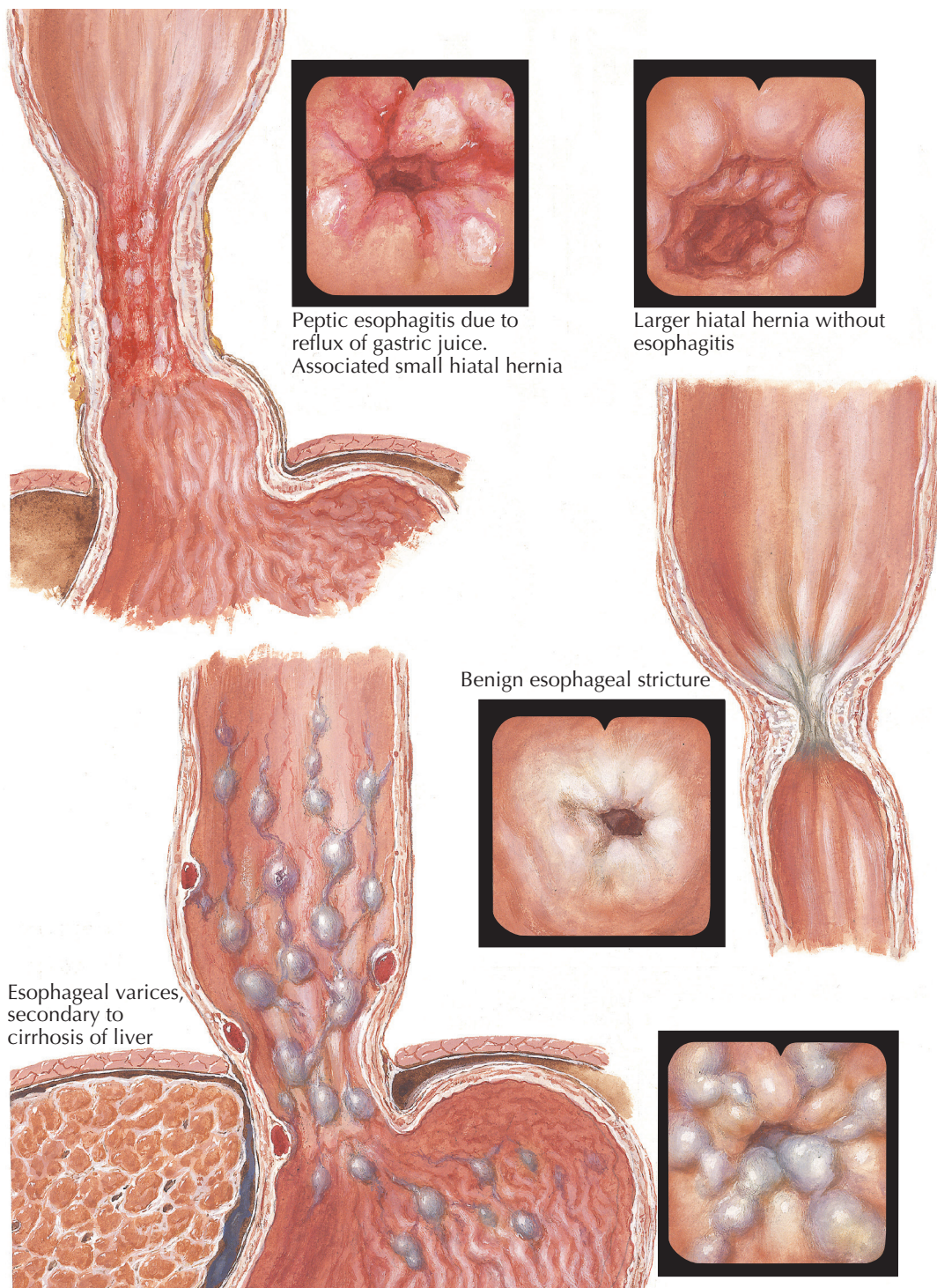
NARROW BAND IMAGING

Although endoscopy has revolutionized the practice of medicine, it is confined by its ability to recognize lesions that appear abnormal only through white light inspection. It is limited in visualization of more subtle but important mucosal abnormalities such as dysplasia. One of the major ongoing refinements of standard endoscopy is using enhanced imaging techniques to visualize mucosal patterns in greater detail. Narrow band imaging (NBI) is a technique in which a filter is used in the endoscope to enhance light wavelengths

for blue and green. These colors are used to enhance visualization of blood vessels through uptake of these wavelengths by hemoglobin. With more detailed imaging of changes in mucosal vascularity and mucosal patterns around these vessels, there is greater accuracy in differentiating hyperplasia from dysplasia as well as different grades of dysplasia and cancer. Studies have shown that in premalignant conditions such as Barrett esophagus, use of NBI improves the diagnostic capability of endoscopy and allows for targeted biopsies of suspicious lesions seen with NBI but not white light endoscopy.

CONFOCAL LASER ENDOMICROSCOPY

Confocal laser endomicroscopy (CLE) is a probe-based technique in which the application of a laser blue light to the mucosal epithelium yields an image that is nearly as precise as a histologic image. The probe is passed through the endoscope and embedded in areas of suspected mucosal abnormalities. A dye is used to highlight cellular structures such as the nuclei or cytoplasm, depending on the dye used. Evolving technology, known as volumetric laser endomicroscopy, is focusing on a means of broader mucosal imaging rather than point-directed visualization. Similar to NBI, the goal of CLE is to give further detail on cellular and tissue morphology, particularly in detecting dysplasia.



Peptic esophagitis due to reflux of gastric juice. Associated small hiatal hernia

Larger hiatal hernia without esophagitis

Benign esophageal stricture

Esophageal varices, secondary to cirrhosis of liver

ESOPHAGEAL VARICES

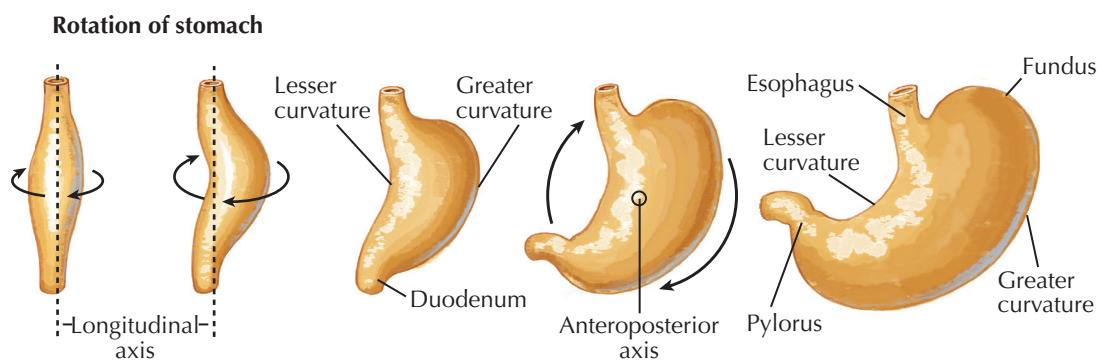
Esophageal varices develop in response to an increase in venous pressure in a location distal to the azygos vein and the right ventricle. The impedance to flow may be functional, as in a hyperdynamic circulatory state, or mechanical, as with a blood clot or tumor. Further vasodilation of the splanchnic venous system may also result from secondary changes in vascular circulatory mediators such as nitric oxide and vasoactive intestinal peptide. A variety of disorders, ranging from splenic, portal, or hepatic vein thrombosis (Budd-Chiari syndrome) to right-sided heart failure, may lead to esophageal varices. The most common cause of esophageal varices is portal hypertension secondary to intrahepatic causes, such as cirrhosis. In cirrhosis, there is fibrosis of the sinusoids and shunting that leads to portal vein backflow. As many as half of patients presenting with a new diagnosis of hepatic cirrhosis have esophageal varices on initial evaluation. The vast majority of patients with cirrhosis will also develop esophageal varices over the course of the disease if they do not undergo liver transplantation. If varices are present, there is a greater risk for bleeding with risk factors such as larger varices, increased portal hypertension, hepatic failure, and endoscopic signs of recent or impending bleeding (e.g., *red wale signs*). Bleeding from esophageal varices may be brisk and massive, and the risk of death is considerable.

Many treatments are available for esophageal varices and are used on the basis of whether they are needed for management of acute bleeding, prevention of recur-

rent bleeding, or prophylaxis in patients with diagnosed nonbleeding varices. Amongst these clinical scenarios, treatments are divided into the broad categories of variceal obliteration (endoscopic banding and sclerosis), pharmacologic reduction of portal venous pressure (beta-antagonists, nitrates, somatostatin), and mechanical reduction of portal venous pressure (transhepatic intravascular portosystemic shunt [TIPS], surgical portacaval shunt, liver transplantation). Acute and chronic

treatments may be a combination of obliterative and pharmacologic treatments. For example, acute bleeding may be managed by esophageal variceal banding and intravenous octreotide, whereas chronic prevention may rely on banding and use of beta-antagonists. Prophylactic therapy tends to be pharmacologic, but obliterative techniques may be used in addition. Therapies such as TIPS and transplant are reserved for more severe and/or refractory cases of variceal bleeding.

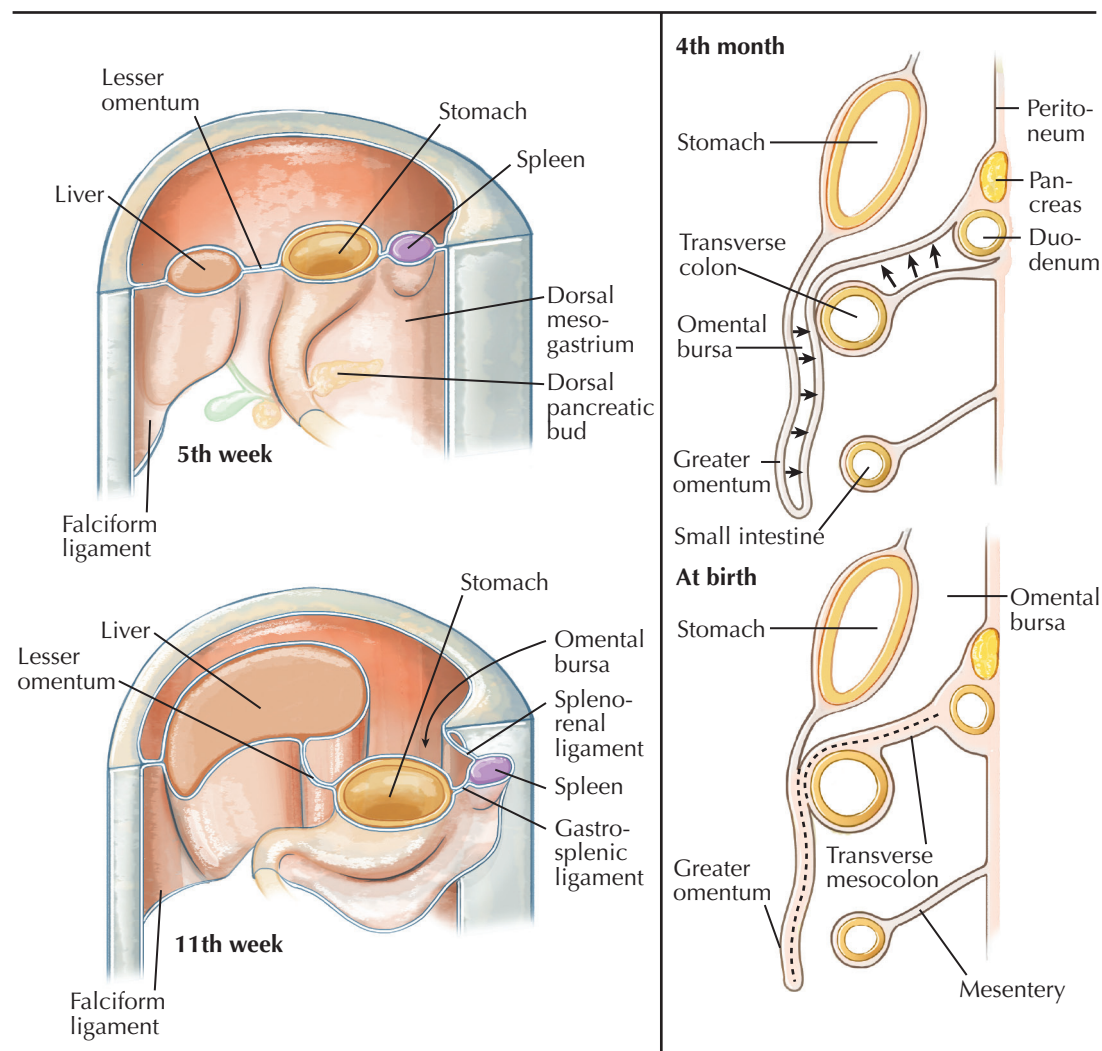
STOMACH



DEVELOPMENT OF STOMACH AND GREATER OMENTUM

The foregut begins as a simple, midline, tubular structure lined by epithelium derived from endoderm. While the endoderm creates the lining of the stomach, the visceral mesoderm that surrounds it will form the muscles, connective tissues, and mesenteries that are associated with the organ. The portion of the foregut that will become the stomach first starts to expand in the sagittal plane, ballooning outward on its anterior and posterior surfaces. However, the expansion of the posterior surface quickly outpaces the other side and the stomach begins to bend. The enlarged expansion of the posterior side will become the stomach's greater curvature, and the anterior side will become the lesser curvature. As this is happening, the presumptive stomach rotates so that the posterior side shifts toward the left of the body and the right side shifts to the right. The rotation and expansion of the posterior side are what give the stomach its characteristic shape, with the esophagus entering just to the right of the fundus and greater curvature, whereas the outlet of the stomach, the pyloric region, shifts to the right and slightly superior to the greater curvature. This moves the stomach from a superior/inferior axis to more of a right/left axis within the abdomen. The inner, circular layer of muscle at the terminus of the stomach enlarges significantly to form the pyloric sphincter.

The rotation and expansion of the stomach do not occur in isolation. The foregut is attached to the posterior body wall by a *dorsal (posterior) mesentery*, in which the spleen and part of the pancreas will develop. The section of this mesentery between the developing spleen and the stomach will become the *greater omentum*. Anteriorly the stomach is connected to the liver, and thereafter, to the anterior body wall by a *ventral (anterior) mesentery*. The section of the ventral mesentery that attaches the liver to the anterior body wall will become the *falciform ligament*, and the section between the liver, stomach, and duodenum will form the *lesser omentum*. As the stomach's posterior surface expands and rotates to the left, the attached mesentery follows, so that the spleen lies along the left side of the abdominal cavity. The dorsal mesentery between the stomach and spleen expands, folding onto itself and creating a large pocket (*omental bursa*) between the two folds. Continued rotation and expansion of the greater



curvature bring this double-layered "apron" to extend inferiorly from the stomach, falling anterior to the transverse colon and small intestines. The space between the two folds is termed the *inferior recess of the omental bursa*; however, this space typically disappears as development proceeds and the two folds adhere and create a single greater omentum. As the liver grows, the stomach shifts to the left side of the abdomen and the liver shifts to the right side. This brings the omental bursa to lie anterior to the pancreas, inferior to the

inferior surface of the liver, and posterior to the stomach and lesser omentum, which can be subdivided into the *hepatogastric* and *hepatoduodenal ligaments*. Occasionally, the omental bursa can extend superiorly and posteriorly to the liver as the *superior recess of the omental bursa*. In its mature form, the omental bursa is isolated from the rest of the abdominal cavity except for a small opening called the *omental foramen*, located immediately posterior to the right edge of the hepatoduodenal ligament.

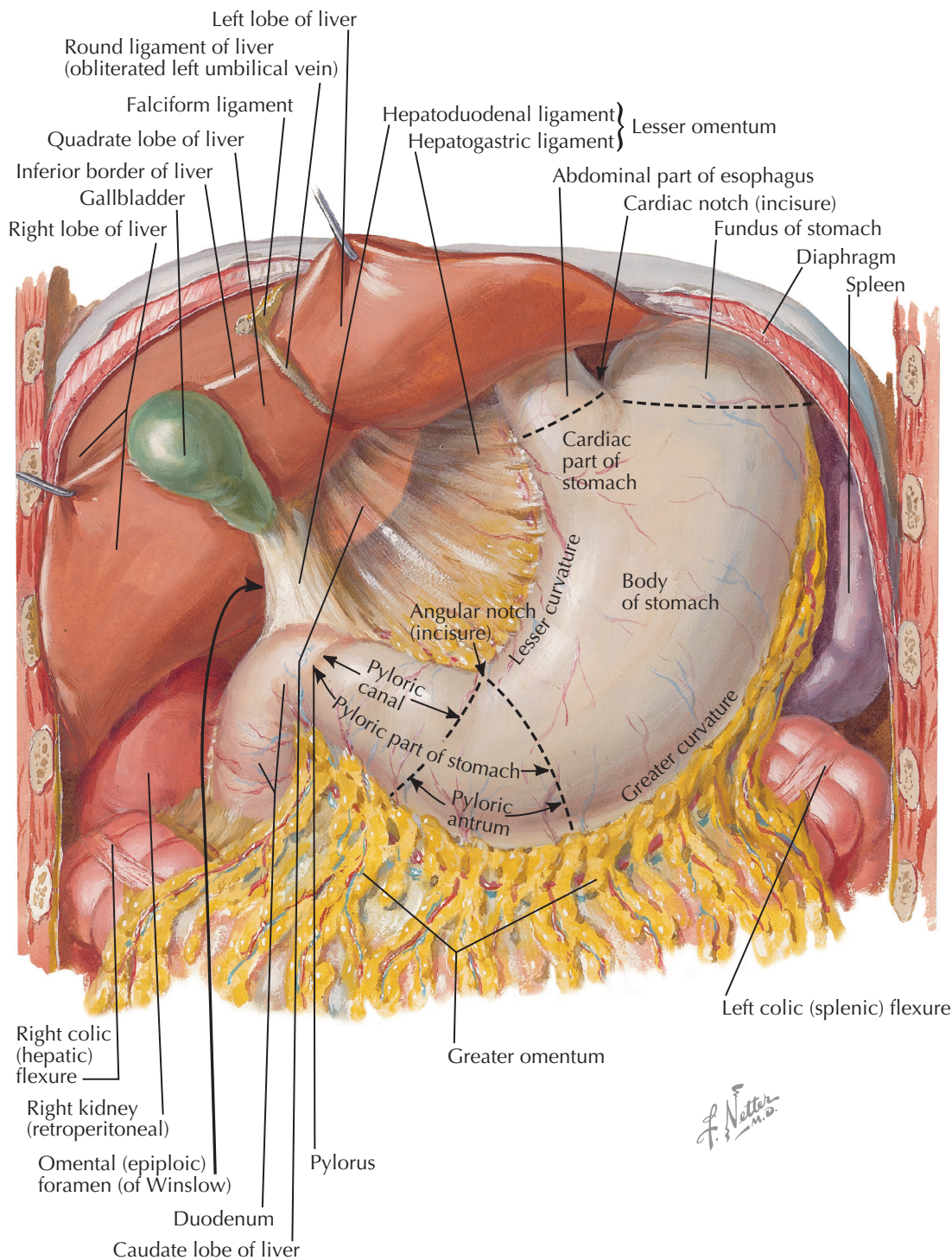
Ed. Palanzo CMI

ANATOMY, NORMAL VARIATIONS, AND RELATIONS OF STOMACH

The stomach is an enlarged reservoir of the proximal digestive tract, in which ingested food is soaked in gastric juice containing enzymes and hydrochloric acid and then released spasmodically into the duodenum by gastric peristalsis. The form and size of the stomach vary considerably, depending on the position of the body and the degree of filling.

The stomach has *anterior* and *posterior* walls that practically touch when the organ is empty and flattened. It is distended inferiorly and to the left, creating a convex *greater curvature* and a concave *lesser curvature* along its superior border. The superiormost region of the greater curvature includes the *fundus* of the stomach, a domed section on the superior left side of the abdomen, which is closely related to the diaphragm and spleen. The greater and lesser curvatures meet at the *cardiac region of the stomach*, where the esophagus enters. On the right the esophagus continues smoothly into the lesser curvature, but on the left there is a definite indentation, the *cardial notch (incisure)*, which becomes most obvious when the fundus is full and bulges superiorly. The largest region of the stomach is the *body (corpus) of the stomach*, located inferior to the cardiac region and fundus. The massiveness of the greater curvature causes the stomach's lumen to shift to the right side of the abdomen, where it will empty into the duodenum. Prior to its terminus, the body of the stomach blends imperceptibly into the *pyloric part*, except along the lesser curvature, where the *angular incisure (notch)* marks the boundary between the body and the pyloric part. The latter contains the *pyloric antrum*, which narrows into the *pyloric canal*, terminating at the *pyloric valve*.

The surface of the stomach is entirely covered and suspended by peritoneum. A double layer of peritoneum, deriving from the embryonic ventral mesentery, extends from the lesser curvature and first part of the duodenum toward the liver. This is the *lesser omentum*, and it may be subdivided into a larger, thinner, *hepatogastric ligament* and a smaller, thicker, distal *hepatoduodenal ligament*, which attaches to the pyloric region and to the upper horizontal portion of the duodenum. The portal vein, proper hepatic artery, and common bile duct are found within the hepatoduodenal ligament. The free edge of the hepatoduodenal ligament, located on the right end of the lesser omentum, forms the anterior border of the *omental (epiploic) foramen (of Winslow)*, which gives access to the *omental bursa* (lesser sac) located posterior to the stomach. The *greater*



omentum, a derivative of the embryonic dorsal mesentery, passes inferiorly from the greater curvature and contains, between its two frontal and two dorsal sheets, the inferior recess of the omental bursa. Typically this space is negligible and the entire greater omentum can be moved like a single apronlike object hanging from the greater curvature.

The anterior surface of the stomach contacts the peritoneum lining the anterior abdominal wall, the inferior surface of the left lobe of the liver, and, to some

extent in the pyloric region, the quadrate lobe of the liver and the gallbladder. Its posterior surface is in apposition with retroperitoneal structures (pancreas, splenic vessels, left kidney, and adrenal gland) from which, however, it is separated by the omental bursa. The fundus of the stomach bulges against the left diaphragmatic dome. On the left, adjacent to the fundus, is the spleen, which is connected to the stomach by the *gastrosplenic ligament*, also derived from the embryonic dorsal mesentery.

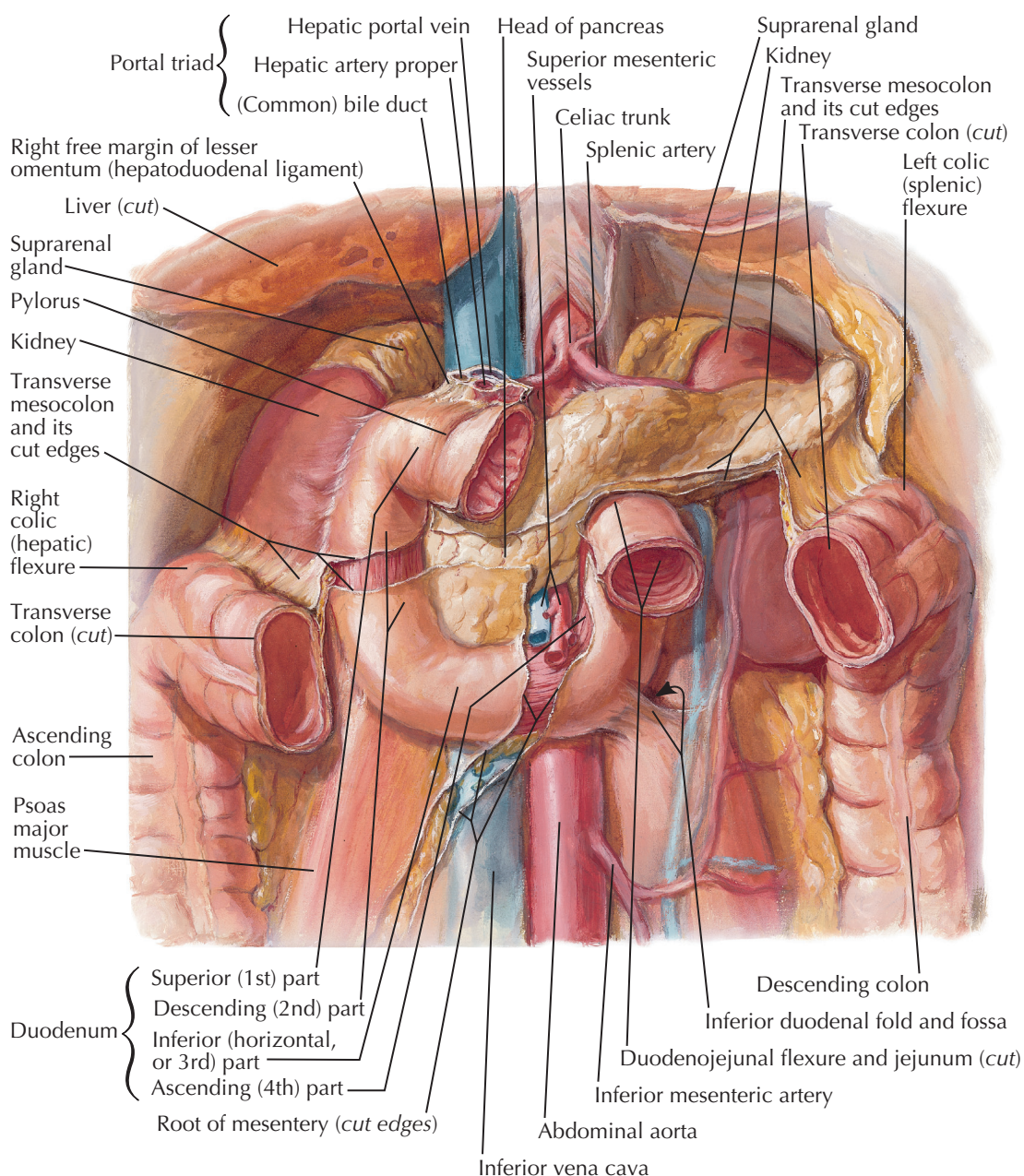
ANATOMY AND RELATIONS OF DUODENUM

The duodenum, the first part of the small intestine, has a total length of about 25 to 30 cm (approximately the width of 12 fingers; hence its name) and is shaped like a horseshoe with the open end facing to the left.

The *superior (first) part*, lying at the level of the first lumbar vertebra, extends horizontally from the pylorus of the stomach to the *superior duodenal flexure*. As a result of being attached to the hepatoduodenal ligament, this first duodenal portion has limited mobility and can adapt its course according to the filling condition of the stomach. The anterior and superior surfaces of the first half of this duodenal segment are in close relation to the inferior surface of the quadrate lobe of the liver and the gallbladder. The radiographic designation “duodenal bulb” refers to the most proximal end of the superior part of the duodenum, which is slightly dilated when the organ is filled and then more sharply separated from the stomach because of the pyloric contraction. The two layers of peritoneum that cover the anterosuperior and posteroinferior surfaces of the duodenum fuse superiorly to form the hepatoduodenal ligament, which contains the *portal triad*. This triad contains the *portal vein*, *proper hepatic artery*, and *common bile duct*. The head of the pancreas is positioned posterior to the first portion of the duodenum, with the two organs being separated by a peritoneal fold of the omental bursa.

The *descending (second) part* of the duodenum extends vertically from the superior to the *inferior duodenal flexure*, which lies approximately at the level of the third lumbar vertebra. The superior portion of the descending duodenum rests laterally upon the hilus of the right kidney, while medially its whole length is attached by connective tissue to the duodenal margin of the pancreatic head. About halfway, the descending portion is crossed anteriorly by the line of attachment of the transverse mesocolon. The portal triad is located posterior to the superior part of the duodenum and continues its course between the descending portion and the head of the pancreas to its opening at the *major duodenal papilla (of Vater)*. This topographic relationship explains the danger of an obstruction of the duct in the presence of a tumor of the pancreatic head.

The *inferior (third, or horizontal) part* of the duodenum begins at the inferior duodenal flexure. It runs horizontally or sometimes in a slightly ascending direc-



tion until it reaches the region of the left border of the aorta, where, curving cranially, it changes direction to pass into the terminal, *ascending (fourth) portion* of the duodenum. Whereas the inferior part of the second portion and the inferior flexure lie over the psoas major of the right side of the body, the inferior duodenum, with its horizontal segment, passes over the vena cava and the abdominal aorta. The superior mesenteric vessels, before entering the root of the mesentery, cross

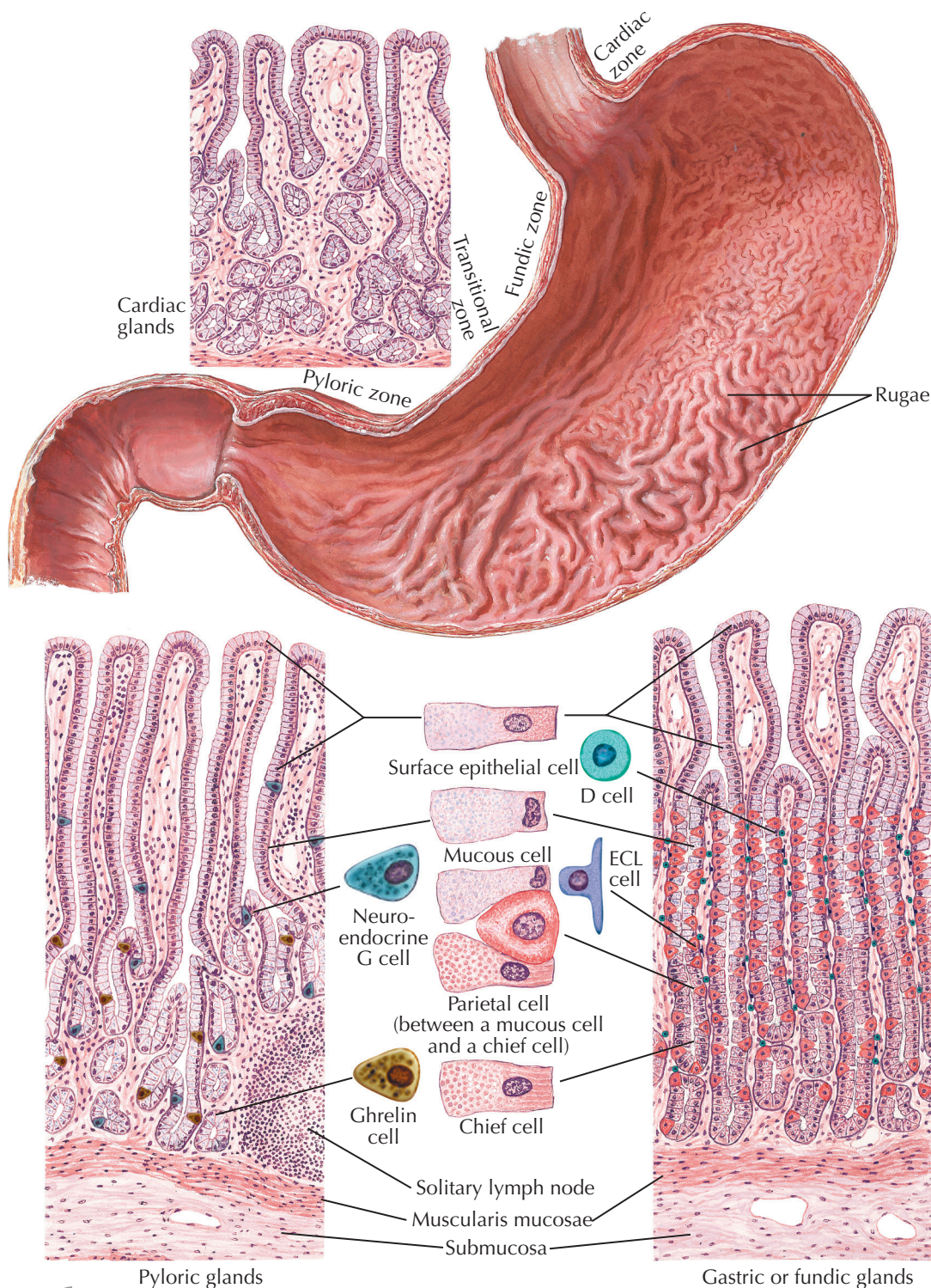
over the inferior part of the duodenum near its transition to the ascending part. The third portion is retroperitoneal, but it becomes increasingly covered by the peritoneum, and the ascending duodenum gains a small mesentery, becoming intraperitoneal as it approaches the *duodenojejunal flexure*. The duodenojejunal flexure is located inferior to the transverse mesocolon at the level of the second lumbar vertebra or of the disc between L1 and L2.

MUCOUS MEMBRANE OF STOMACH

The reddish-gray mucous membrane of the stomach, composed of a surface layer of epithelial cells, the lamina propria, and the muscularis mucosae, commences at the cardia along an irregular or zigzag line (referred to as the Z line). Deep to the mucosa is the submucosa and three external muscle layers of the stomach. When the stomach is empty, the mucosa appears to be formed of folds (*rugae*), which flatten considerably when the stomach is distended. In the region of the lesser curvature, where the mucosa is more strongly fixed to the underlying muscular layer, the folds take a longitudinal course. The rugae are generally smaller in the fundus and become larger as they approach the pyloric portion of the stomach, where they show a tendency to run diagonally across the stomach toward the greater curvature. Besides these broad folds, the gastric mucosa is further characterized by numerous shallow invaginations, which divide the mucosal surface into a mosaic of elevated areas varying in shape. When viewed under magnification, several delicate ledges, or *mammillated areas*, and depressions, known as *gastric pits*, can be seen. Gastric glands empty into the stomach lumen through the gastric pits.

The gastric epithelium consists of a single layer of simple columnar cells, and it is sharply demarcated from the stratified squamous epithelium of the esophagus at the gastroesophageal junction in the cardiac area of the stomach. The columnar epithelial cells are of the mucoid type and contain mucigen granules in their outer portions and a single ovoid nucleus at their base. These cells line the tubular cardiac glands along with mucoid neck, chief, parietal, and enteroendocrine cells that allow the stomach to carry out its functions.

1. The *cardiac glands* are confined to a narrow zone, 0.5 to 4 cm in width, around the cardiac orifice. They are coiled and are lined almost entirely by mucus-producing epithelial cells.
2. The gastric, or *fundic*, glands are located in the fundus and over the greater part of the body of the stomach. They are fairly straight, simply branched tubules, with a narrow lumen reaching down almost to the muscularis mucosae. They are lined by four types of cells: (1) The *mucoid neck cells* are the same as seen in the cardiac region but differ from the cells of the surface epithelium in that their mucigen granules have slightly different staining qualities and their nuclei tend to be flattened or concave at the base of the cells. (2) The *chief cells* are found primarily in the lower half of the glands. They have a spherical nucleus and contain light-refracting granules and a Golgi apparatus, the size and form of which vary with the state of secretory activity. They produce pepsinogen, the precursor of pepsin, a digestive enzyme. (3) *Parietal cells* are larger and usually clustered away from the gland's lumen, to which they connect by small gaps stemming from intracellular canaliculi. Their intraplasmatic granules are strongly eosinophilic; they refract light less than chief cells do. Parietal cells produce the hydrochloric acid that lowers the pH in the stomach. They also produce intrinsic factor, a glycoprotein that allows vitamin B₁₂ to be absorbed further along in the ileum of the gastrointestinal tract. (4) *Enteroendocrine cells* are isolated glandular cells that release hormones into the lamina propria to modulate activity of the stomach



and other digestive organs. Each enteroendocrine cell in the stomach may secrete gastrin (C cells), ghrelin, bombesin, enkephalins, vasoactive intestinal peptide, or somatostatin (D cells). *Enterochromaffin-like cells* secrete histamine, and *enterochromaffin cells* secrete serotonin. Different hormones are released by enteroendocrine cells elsewhere in the gastrointestinal tract.

3. The *pyloric glands* are located in the *pyloric region* but also spread into a *transitional zone*, in which

both gastric and pyloric glands are found and which extends diagonally and distally from the lesser to the greater curvature. The tubes of the pyloric glands are shorter, more tortuous, and less densely packed, and their ends are more branched than the fundic glands. Pyloric gland pits are markedly deeper than those in other regions and are lined primarily by mucous cells (as in the cardiac region); occasional parietal or enteroendocrine cells may also be seen.

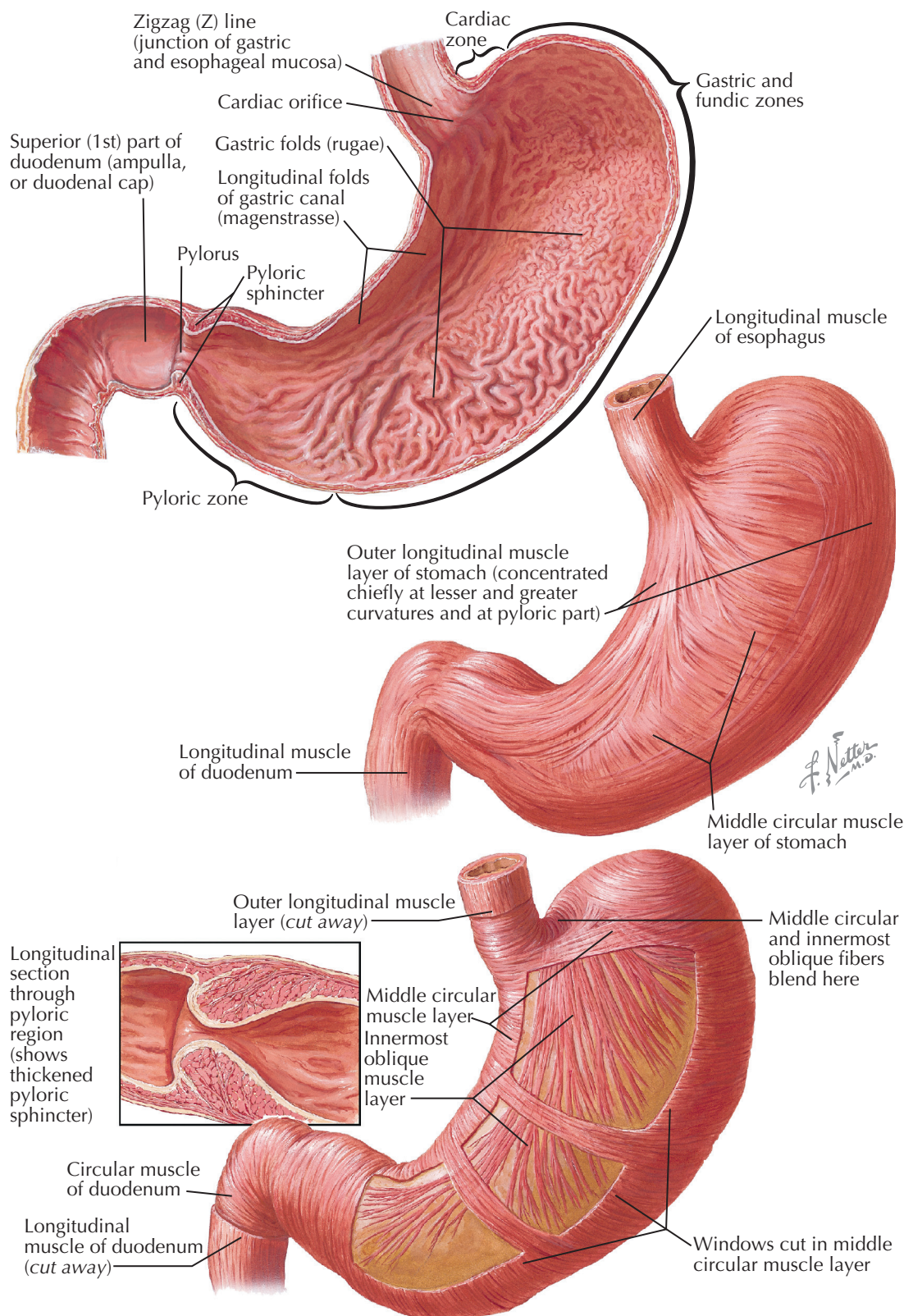
MUSCULATURE OF STOMACH

The musculature of the gastric wall consists solely of smooth muscle fibers, which, in contrast to the dual-layered arrangement elsewhere in the digestive tract, exist in three distinct layers. Only the middle circular layer covers the wall completely; the other two layers, the superficial longitudinal and deepest oblique layers, are present as incomplete coats. The longitudinal and circular layers are interconnected by continuous fibers, as are the circular layer and the deepest oblique muscular coats.

The *longitudinal layer* of the stomach is continuous with the longitudinal muscle layer of the esophagus, which divides at the cardia into two stripes. The stronger of these muscle bands follows the lesser curvature across the superior border of the stomach. The other set of fibers is somewhat broader but thinner as it migrates along the fundus, across the greater curvature toward the pylorus. Thus, the middle areas of the anterior and posterior surfaces of the stomach remain mostly free of longitudinal muscle fibers. The marginal muscle fibers of the upper longitudinal muscle stripe radiate obliquely toward the anterior and posterior surfaces of the fundus and corpus to unite with fibers of the circular layer. In the pyloric area, the two bands of longitudinal muscle fibers converge again to form a uniform layer, which, to a great extent is continuous with the external, longitudinal muscular layer of the duodenum. It is the increased thickness of the longitudinal muscle layer in the anterior and posterior parts of the pylorus that is responsible for the so-called pyloric ligaments (anterior and posterior pyloric ligaments, respectively).

The *circular layer* of smooth muscle is not only the most continuous but the strongest of the stomach's three layers. It also begins at the cardia as the continuation of the superficial fibers of the circular esophageal muscle. The circular layer becomes markedly more pronounced as it approaches the pylorus, forming the pyloric sphincter.

The innermost layer is formed by *oblique fibers* of the smooth muscle layer; it is most strongly developed in the region of the fundus and becomes progressively weaker as it approaches the pylorus. In the cardiac region, its fibers connect with the deeper circular layers of the esophageal muscle. No oblique fibers exist in the vicinity of the lesser curvature, but the fibers closest to it arise from a point to the left of the cardia and run parallel to the lesser curvature. There are longitudinal furrows in the lesser curvature caused by the absence of this innermost oblique layer. The oblique fiber bundles, following these first more or less longitudinal fibers, bend farther and farther to the left and, finally, become practically circular in the region of the fundus, where their continuity with the fibers of the circular layer is clearly evident. Because the oblique fibers of the anterior and posterior walls merge into one another in the region of the fundus, the oblique layer as a whole is made of U-shaped loops. The oblique fibers never reach the greater curvature in the region of the corpus but fan out and gradually disappear in the walls of the stomach. To the left of the esophagus the oblique fibers form *slings* that project from the anterior wall of the stomach to the posterior wall, making a tight bend around the cardiac notch. On the opposite side of the cardiac region, the circular layer has substantial *clasp fibers* that pinch and narrow the cardiac region. Acting



together, the sling and clasp fibers help prevent gastric reflux and form a functional, but not anatomic, lower esophageal sphincter.

MUSCULATURE OF PYLORIC SPHINCTER

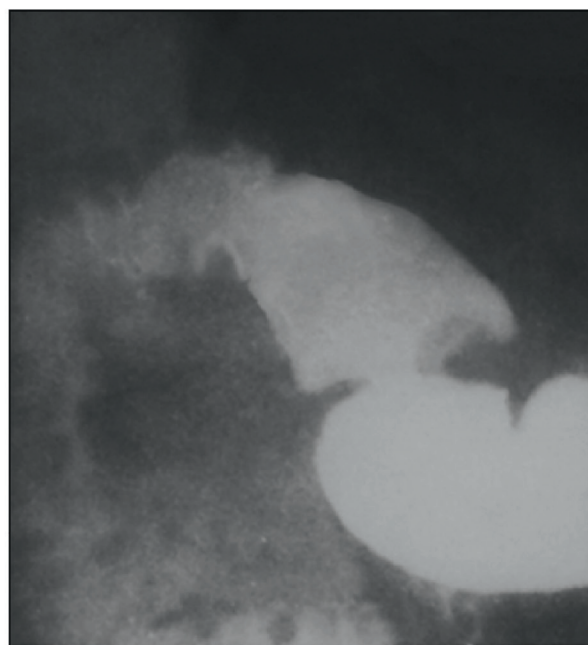
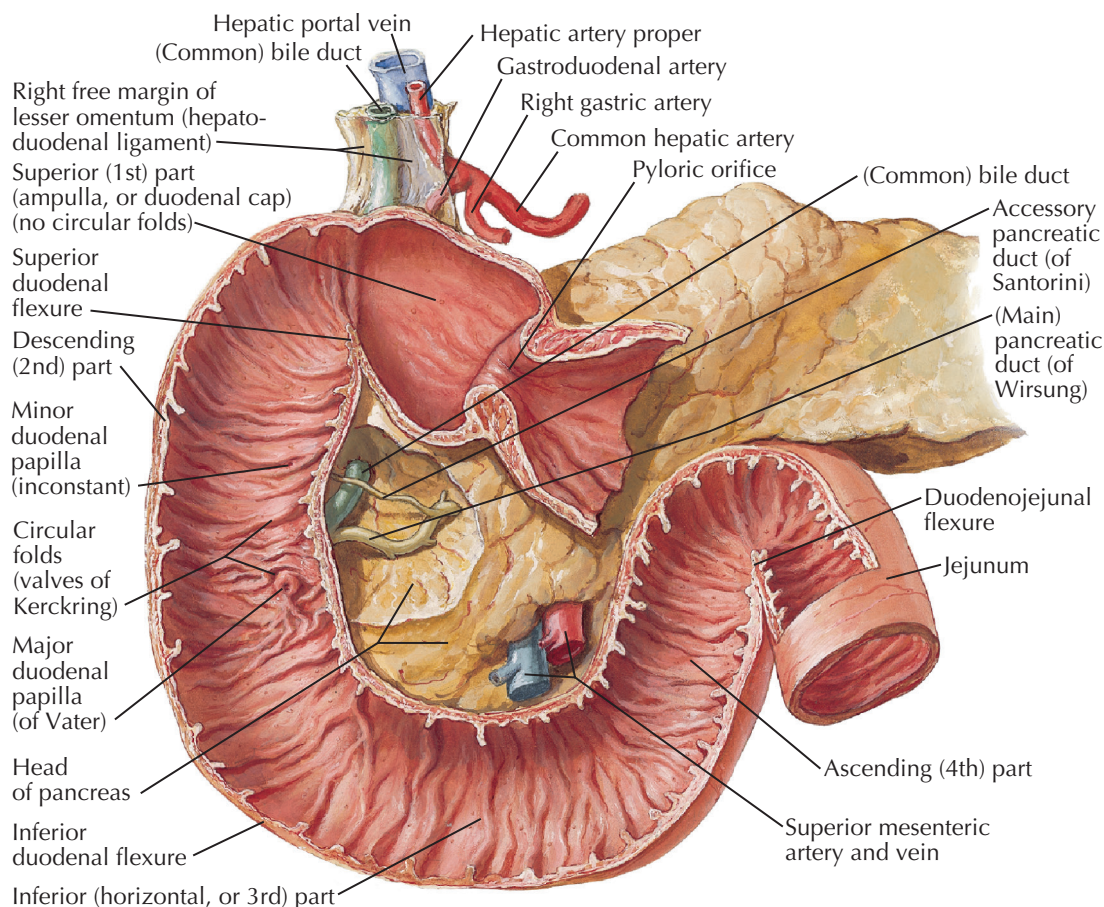
The middle circular layer thickens considerably at the pylorus, forming a muscular ring that acts as a true anatomic sphincter. The pyloric sphincter is not con-

tinuous with the circular musculature of the duodenum but is separated from it by a thin, fibrous septum of connective tissue. A few fibers of the longitudinal muscle layer, the greater mass of which, as mentioned above, is continuous with the corresponding layer of the duodenum, contribute also to the muscle mass of the pyloric sphincter; they may even find their way into the network of the sphincter bundles and penetrate as far as the submucosa.

DUODENAL BULB AND MUCOSAL SURFACE OF DUODENUM

The mucosa of the widened first portion of the duodenum, known also as the *duodenal ampulla* (cap, bulb), is relatively flat and smooth except for a few small longitudinal folds. Except for the smooth duodenal ampulla, the mucosal surface of the duodenum, which in living subjects is reddish in color, is lined with villi, giving the small intestines their velvety appearance. The mucosa of the distal duodenum is nearly identical to the small intestine with *circular folds (of Kerckring)* projecting into the lumen. These folds, which considerably increase the surface area of the intestine, begin in the region of the superior duodenal flexure, increasing in number and elevation in the more distal parts of the duodenum. They do not always form complete circles along the entire intestinal wall, because some are semicircular or crescent shaped, whereas others branch out to connect with adjacent folds. Very often they deviate from their circular pattern and pursue a more spiral course. The circular folds are large macroscopic structures and include mucosa and submucosa in their core. The more superficial layers of the duodenum, the muscularis externa and adventitia, are not included in the circular folds.

Approximately halfway down the posteromedial aspect of the descending part of the duodenum, a distance of approximately 8.5 to 10 cm from the pylorus, is located the *major duodenal papilla*, also known as the *papilla (of Vater)*. This is where the *common bile duct* and the *major pancreatic duct (of Wirsung)* open into the duodenum. The common bile duct approaches the duodenum within the enfolding hepatoduodenal ligament of the lesser omentum and continues inferiorly in the groove between the descending portion of the duodenum and the pancreas. The terminal part of the common bile duct produces a slight but perceptible longitudinal impression in the posteromedial duodenal wall known as the *longitudinal fold of the duodenum*. This fold usually ends at the papilla but may occasionally continue for a short distance beyond the papilla in the form of the so-called frenulum. Small mouthlike folds at the top of the papilla protect the mouth of the combined bile duct and pancreatic duct. A small, wartlike, and generally less distinct second papilla, the *minor duodenal papilla*, is situated about 2.5 cm above and slightly medial to the major papilla. It serves as an opening for the *minor pancreatic duct (of Santorini)*.



Normal duodenal bulb

The duodenal ampulla, varying in form, size, position, and orientation, appears in an anteroposterior radiograph as a triangle, with its base at the pylorus and its tip pointing toward the superior flexure of the duodenum. The duodenum's longitudinal folds, as well as the circular folds in the lower parts of the duodenum, can be visualized radiographically if a barium meal of appropriate quantity and consistency is given. In such

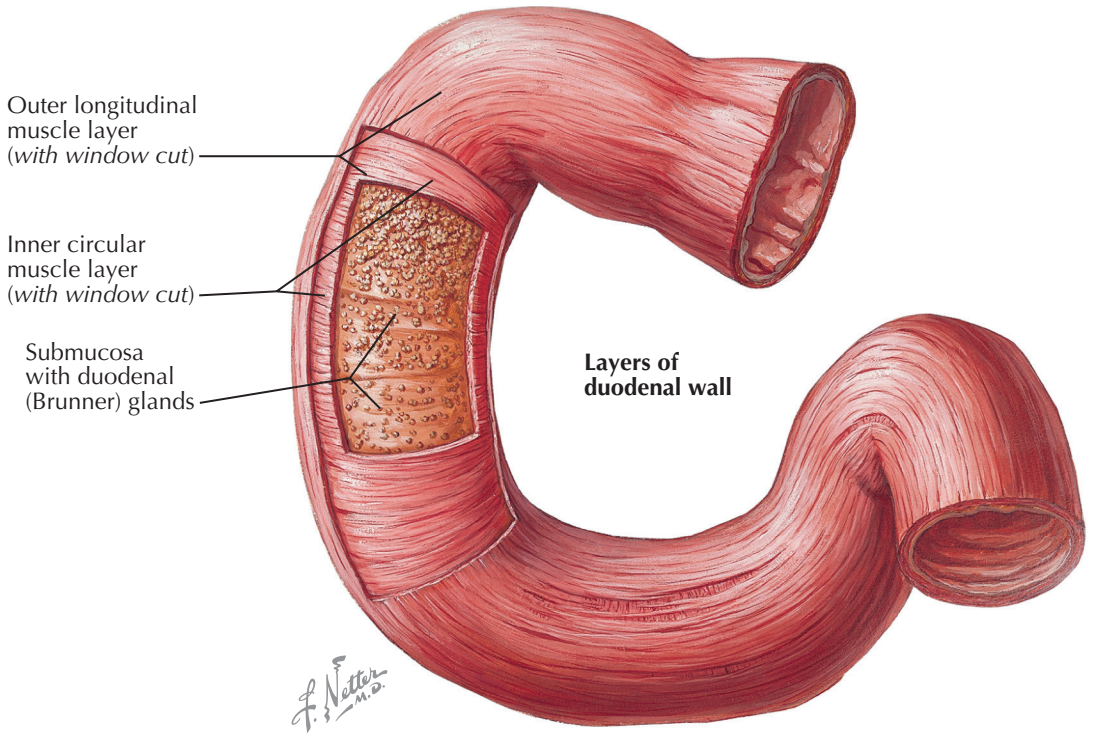
a relief picture of the mucosa, the region of the major duodenal papilla occasionally appears as a small, roundish filling defect. When the papilla is enlarged in the form of a small diverticulum, the contrast medium may sometimes enter the terminal portions of the bile and pancreatic ducts, with the result that on the x-ray, this area looks like the shape of a molar tooth with two roots.

STRUCTURES OF DUODENUM

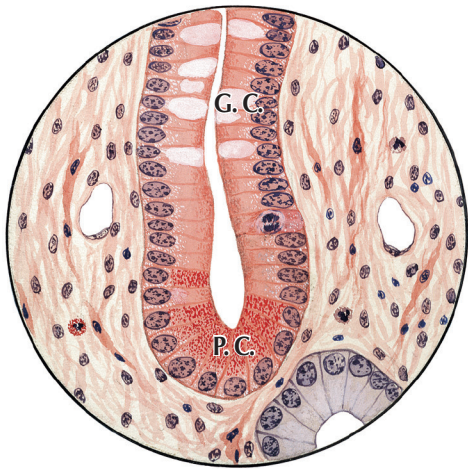
The duodenum is part of the gastrointestinal tract and as such it is composed of a *mucosa*, *submucosa*, *muscularis externa*, and *adventitia/serosa*. The duodenum has a serosal covering wherever it is covered by peritoneum and an adventitia elsewhere. It is part of the small intestine, but it is embryonically, morphologically, and functionally distinct from the jejunum and ileum. Aside from the duodenal ampulla, the duodenum displays the macroscopically visible circular folds (of Kerckring), which project into the lumen and increase the available surface area. These circular folds contain cores of mucosa and submucosa. At the microscopic level, the surface area of the mucosa is extensively increased by the presence of *villi*, small fingerlike projections of the mucosa into the lumen. In between villi are the *intestinal glands (crypts of Lieberkühn)*, which project toward the submucosa. The villi of the duodenum are very dense, large, and, in some areas, leaflike. At the core of each villus is a clear area called a *central lacteal* that transports lymphatic fluid and fat-soluble substances from the small intestines.

The mucosa can be subdivided into a surface *epithelium*, *lamina propria*, and *muscularis mucosae*. The epithelium of the duodenal mucosa consists of a single layer of high columnar cells, *enterocytes*, with a marked cuticular border. Between enterocytes are a significant number of mucus-releasing *goblet cells*. In the depths of the crypts, there are cells filled with eosinophilic *Paneth cells* as well as some enteroendocrine cells. The lamina propria consists of loose connective tissue located deep to the epithelial lining. Many cells, such as plasma cells and lymphocytes, migrate in and out of the lamina propria in response to immune signals. Deep to the lamina propria is the muscularis mucosae, a double layer of smooth muscle cells, the fibers of which enter the lamina propria and continue to the tips of the villi, enabling the latter to pump fluid from their central lacteals.

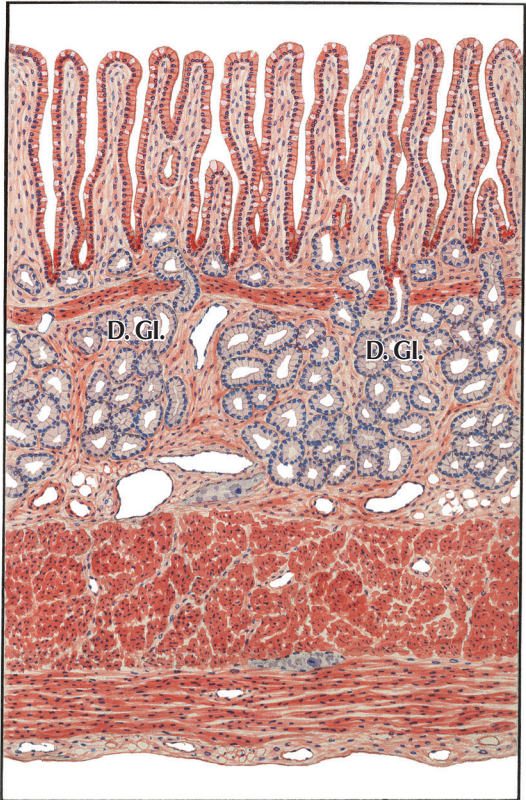
The submucosa, lying between the mucosa and the muscularis externa, makes it possible for these two layers to shift in relation to each other. It is made up of dense irregular connective tissue, the fibers of which are arranged in a mesh. In this network are embedded the *duodenal glands (of Brunner)*, characteristic of the duodenum. These are tortuous acinotubular glands with multiple branches at their ends; breaking through the muscularis mucosae, they open into the intestinal crypts. Cells of the duodenal glands release zymogen granules, mucus, bicarbonate, and alkaline glycoproteins. This fluid helps raise the pH of the gastric contents that enter the duodenum after digestion in the acidic environment of the stomach. This explains why



D. Gl — Duodenal glands
G. C. — Goblet cell
P. C. — Paneth cell



Crypt of Lieberkühn



Longitudinal section through duodenal wall

the duodenal glands are larger and more numerous in the proximal duodenum and diminish in size and density as the duodenojejunal junction is approached. The number of glands is said to be much smaller in older than in younger individuals.

The two-layered muscularis externa of the duodenum is the same as in the jejunum and ileum. An inner circular layer is covered by a thinner outer longitudinal layer. As elsewhere in the small intestine, the *submucosal*

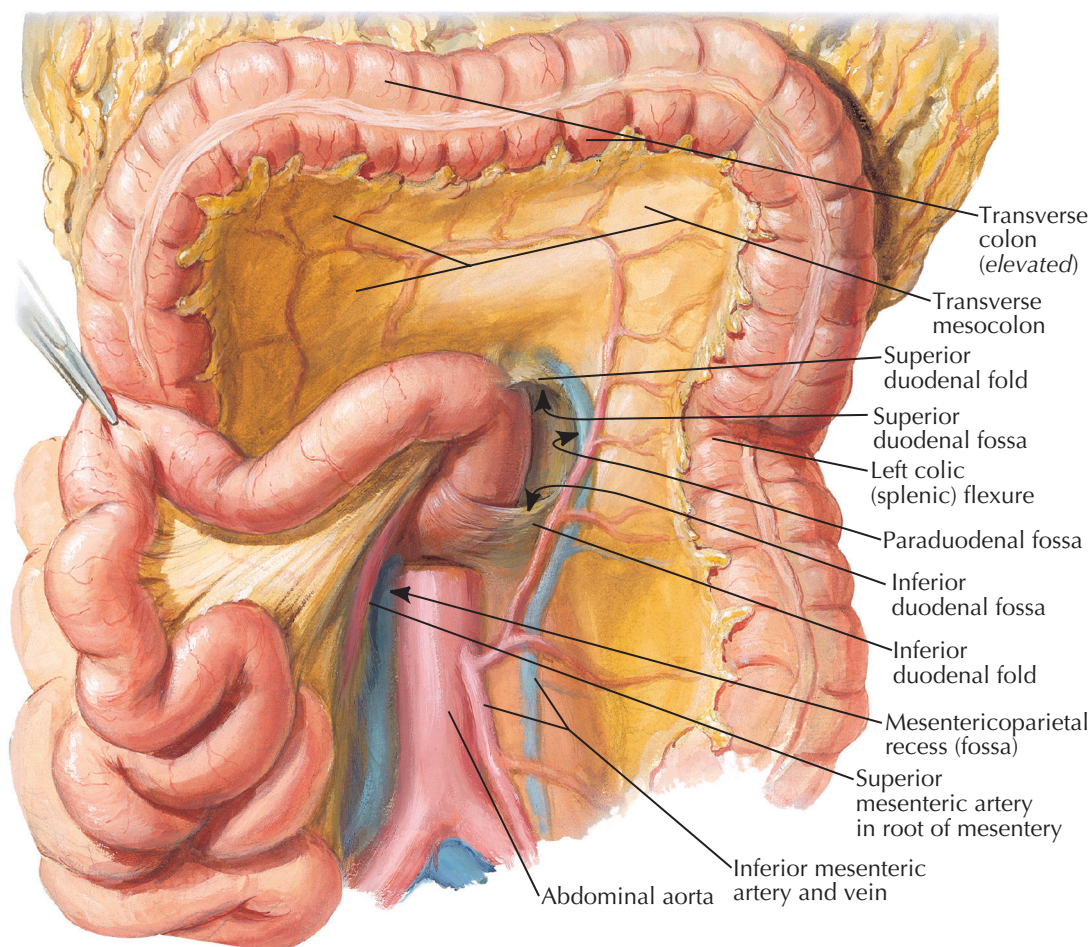
(*Meissner*) plexus of nerves is found in the submucosa near its boundary with the muscularis externa. The *myenteric (Auerbach)* plexus can be located between the circular and longitudinal layers of the muscularis externa. The subserosa and the adventitia are composed of fine collagenous fibrils, which form a delicate lattice. The peritoneum of the duodenum consists, as do all serous membranes of the body, of a layer of flattened mesothelial cells.

DUODENAL FOSSAE AND LIGAMENT OF TREITZ

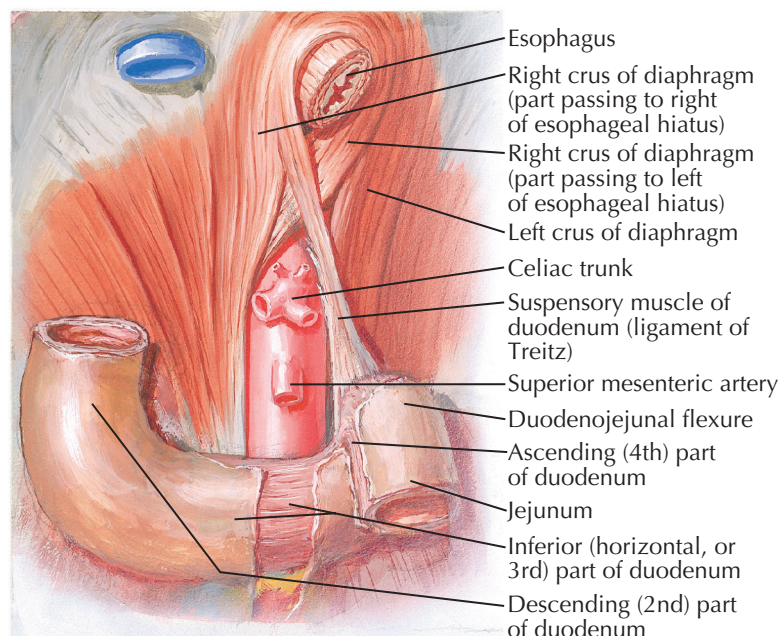
The duodenojejunal flexure lies left of the midline at the level of the first and second lumbar vertebrae. The *suspensory muscle of the duodenum* (ligament of Treitz, suspensory ligament of the duodenum) is a flat, fibromuscular ligament arising from the right crus of the diaphragm near the aortic hiatus. It passes, with individual variations, inferior to the left of the celiac trunk and superior mesenteric artery, posterior to the pancreas, to reach the duodenojejunal flexure. The smooth muscle cells of the ligament are largely continuous with the musculature of the celiac and superior mesenteric arteries; at the intestinal attachment they are connected with the longitudinal muscular layer of the gut, some extending as far as the mesentery of the small intestine. The attachment of the ligament to the duodenum may be quite narrow or it may extend over a considerable portion of the third part of the duodenum. If the suspensory ligament of the duodenum is short, the duodenojejunal flexure is high; if it is long, the flexure may lie so low that the terminal duodenal segment does not take the usual ascending course.

Several peritoneal recesses exist to the left of the ascending portion of the duodenum. These result from secondary fixation of the mesentery of the descending colon to the posterior abdominal wall; they vary greatly in depth and size between individuals. The most important are those arising from the *superior duodenal fold* and the *inferior duodenal fold*. These originate from the point of attachment of the descending mesocolon and run archlike from left to right, the superior to reach the duodenojejunal flexure and the inferior to the ascending portion of the duodenum. The superior fold is inferiorly concave and forms the aperture of the *superior duodenal fossa*, whereas the inferior fold is superiorly concave and forms the aperture of the *inferior duodenal fossa*. These fossae may be clinically significant as sites of intraperitoneal herniation. They are bounded anteriorly by the superior and inferior duodenal folds, respectively, and on the left by the ascending portion of the duodenum or the duodenojejunal flexure. Both fossae are bounded on the right by the parietal peritoneum and extend behind the posterior duodenal wall, which is covered by visceral peritoneum. Near the insertion of the superior duodenal fold is the inferior mesenteric vein, ascending to reach the splenic vein. At the corresponding position in the inferior fold is the ascending branch of the left colic artery. The left ureter can be found immediately posterior to the inferior duodenal fossa.

Several rarer types of fossae may also be found in this region, such as the *paraduodenal recess* bounded by the inferior mesenteric vein and the ascending branch of the left colic artery. In this case, a somewhat longitudinal peritoneal fold, the *paraduodenal fold*, slightly



**Exposure of suspensory
muscle of duodenum
(ligament of Treitz)**



concave to the right, occasionally gives rise to a so-called left duodenal hernia (of Moynihan). This fossa can sometimes be separated into two partial folds; the more ventral and superficial fold rises above the ascending branch of the left colic artery, whereas the deeper or more posterior fold is bordered by the inferior mesenteric vein.

On very rare occasions a duodenojejunal fossa (not illustrated) extends cranially from the duodenojejunal

flexure under the root of the transverse mesocolon, or a *retroduodenal recess* runs superiorly between the aorta and the ascending portion of the duodenum. The *mesentericoparietal fossa*, invariably present in the fetus, occasionally forms the enclosing sac for a right paraduodenal hernia. It is bounded anteriorly by the superior mesenteric vessels as they enter the mesentery of the small intestine, and posteriorly by the parietal peritoneum over the right side of the aorta.

ARTERIES OF STOMACH, LIVER, AND SPLEEN

BLOOD SUPPLY OF STOMACH AND DUODENUM

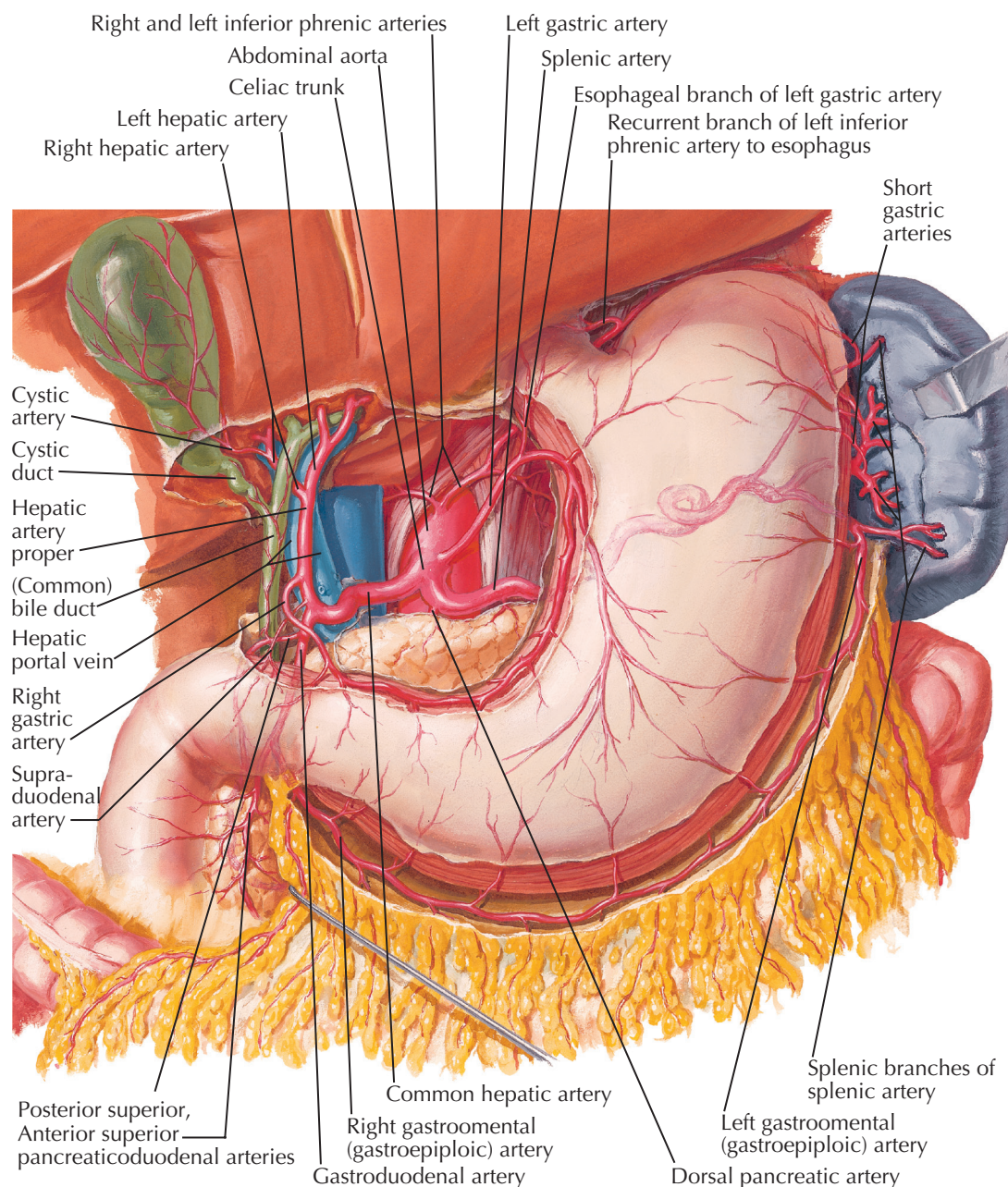
The conventional textbook description of the blood supply to the gastrointestinal organs and the spleen has established the misleading concept that the vascular patterns of these organs are uniform. In fact, they are unpredictable and vary in every instance. In the following account, we will first present the “typical” version of the vascular tree before examining the blood supply to each organ and then some of the common vascular variations that may be encountered in surgical resections.

Typically, the entire blood supply of the foregut organs (liver, gallbladder, stomach, duodenum, pancreas, and spleen) is derived from the *celiac arterial trunk*, a supplementary small portion being supplied by the superior mesenteric artery via its *inferior pancreaticoduodenal branch*. The caliber of the celiac arterial trunk varies from 8 to 40 mm in width. Most typically, it gives off three branches, the *left gastric*, *common hepatic*, and *splenic arteries*, which frequently have the appearance of a tripod (25%).

After branching from the celiac trunk, the *left gastric artery* travels superiorly and to the left. It reflects onto the cardiac region of the stomach and travels along the lesser curvature of the stomach, travelling from left to right. It also gives off an *esophageal branch* that ascends from the cardiac region of the stomach toward the distal esophagus.

The common hepatic artery leaves the celiac trunk and progresses to the right. In the vicinity of the portal vein it divides, sending the *proper hepatic artery* superiorly. The *right gastric artery* is also typically seen leaving this vessel and traveling to the lesser curvature of the stomach, where it will anastomose with the left gastric artery. As it travels superiorly, the proper hepatic artery divides into *right and left hepatic arteries*, which travel into the liver. Before entering the liver, the right hepatic artery most typically gives off the *cystic artery* to the gallbladder. The other branch of the common hepatic artery is the *gastrooduodenal artery*. The small *supraduodenal artery*, which travels to the superior duodenal flexure, most frequently branches from the gastroduodenal artery. This vessel gives off the *posterior superior pancreaticoduodenal artery*, *anterior superior pancreaticoduodenal artery*, and, finally, *right gastroepiploic (gastroepiploic) artery*, which travels along the right side of the greater curvature of the stomach.

The *splenic artery*, the celiac trunk's third branch, is a large, coiled artery that travels to the left of the abdomen superior to, or within, the pancreas. It generally gives off a large *dorsal pancreatic artery* to supply the head and body of the pancreas, along with the *greater pancreatic artery* a bit further down its length. The *artery to the tail of the pancreas* can be seen as a small branch of the distal splenic artery connecting with the greater and dorsal



pancreatic arteries by means of the *inferior pancreatic artery* within the pancreas. Near its terminus, the splenic artery gives off several branches that pierce the hilus of the spleen to supply the organ. As this is happening, the *short gastric arteries* leave the superiormost aspect of the splenic artery to supply the fundus of the stomach. Inferiorly, the *left gastroepiploic (gastroepiploic) artery* leaves the splenic artery to supply the left side of the stomach's greater curvature and anastomose with the right gastroepiploic artery.

The blood supply of the stomach and abdominal esophagus is accomplished by six primary and five secondary arteries. The primary arteries are the (1) right gastric and (2) left gastric, coursing along the lesser curvature; (3) right gastroepiploic and (4) left gastroepiploic, coursing along the greater curvature (each of these four vessels giving off branches to the anterior and posterior surfaces of the stomach, where they anastomose); (5) splenic, which gives off in its distal third a variable number (2 to 10) of short gastric branches, and

BLOOD SUPPLY OF STOMACH AND DUODENUM (Continued)

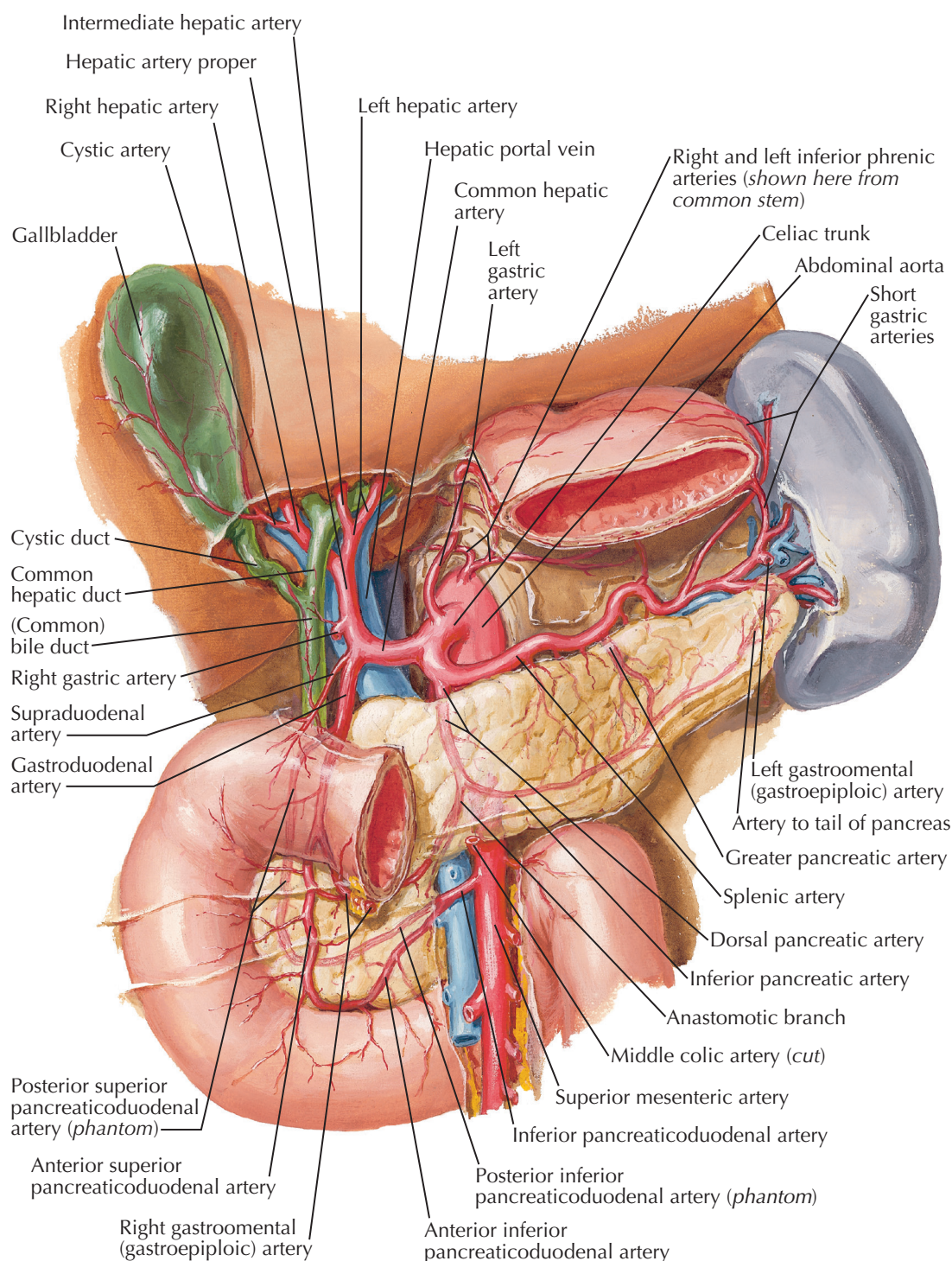
from its superior or inferior terminal division the left gastroomental; and (6) gastroduodenal, by direct small branches (1 to 3) and, frequently, by a large pyloric branch.

The secondary arteries are the (7) anterior superior pancreaticoduodenal (end branch of the gastroduodenal) by short twigs and, frequently, by a large pyloric branch; (8) supraduodenal artery of varied origin (gastroduodenal, posterior superior pancreaticoduodenal, hepatic, right gastric) which, in addition to supplying the first inch of the duodenum, often sends one or more branches to the pylorus; (9) posterior superior pancreaticoduodenal, predominantly the first collateral of the gastroduodenal, which, in its tortuous descent along the left side of the common bile duct to reach the back of the pancreas and duodenum, frequently gives off one or more pyloric branches, the latter, in some instances, uniting with the supraduodenal and right gastric; (10) *dorsal pancreatic artery* of varied origin (splenic, hepatic, celiac, superior mesenteric), the right branch of which anastomoses with the superior pancreaticoduodenal, gastroduodenal, and right gastroepiploic and, in so doing, sends small branches to the pylorus; (11) *left inferior phrenic*, which, after passing inferior to the esophagus in its course to the diaphragm, in most instances gives off a large recurrent branch to the cardioesophageal end of the stomach posteriorly, where its terminals anastomose with other cardioesophageal branches derived from the left gastric, splenic terminals, aberrant left hepatic from the left gastric, and descending thoracic esophageal branches.

This conventional form of the celiac with its three branches occurs in only 55% of the population, for the celiac often lacks one or more of its typical branches. Whether in a complete or incomplete form, the celiac trunk forms a hepatosplenogastric trunk in about 90% of the population. The celiac may omit the left gastric, so that a hepatosplenic trunk is present (3.5%); omit one or more of the hepatic arteries, so that a splenogastric trunk is present (5.5%); or omit the splenic, so that a hepatogastric trunk is present (1.5%). Additional branches may originate from the celiac trunk: the dorsal pancreatic (22%), inferior phrenic (74%), and, occasionally, even the middle colic or an accessory middle colic artery. In many instances the common hepatic artery is absent, being replaced from the superior mesenteric, aorta, or left gastric.

Typically, the *left gastric artery* arises from the celiac (90%), most commonly as its first branch. In remaining cases it arises from the aorta, the splenic or hepatic artery, or a replaced hepatic trunk. Varying in width from 2 to 8 mm it is considerably larger than the right gastric, with which it anastomoses along the lesser curvature. Before its division into anterior and posterior gastric branches, the left gastric supplies the cardioesophageal end of the stomach, either by a single ramus that subdivides or by two to four rami given off in seriation by the main trunk. Accessory left gastric arteries occur frequently. They are (1) a large left gastric from the left hepatic; (2) a large ascending posterior gastroesophageal ramus from the splenic trunk or from the superior splenic polar; or (3) a slender, thread-like cardioesophageal branch from the celiac artery.

ARTERIES OF LIVER, PANCREAS, DUODENUM, AND SPLEEN



aorta, first part of the splenic artery, or inferior phrenic artery.

The terminal branches of the left gastric anastomose with (1) branches of the right gastric; (2) short gastric arteries from the splenic terminals or splenic superior polar or left gastromental; (3) cardioesophageal branches from the left inferior phrenic (via its recurrent branch), an aberrant left hepatic artery from the left gastric (A), or an accessory left gastric from the left hepatic (B) and from descending rami of thoracic

esophageal branches. The degree of anastomosis about the cardioesophageal end of the stomach is variable; it may be very extensive or very sparse.

In about one fourth of the population, the left gastric artery gives off a large left hepatic artery (2 to 5 mm wide, 5 cm long) to the left lobe of the liver. Such a left hepatic may be either replaced or accessory. In the replaced type (12%), no celiac left hepatic is present, the entire blood supply to the lateral segment of the left lobe being derived from the left gastric artery. The

ARTERIES OF STOMACH, DUODENUM, PANCREAS, AND SPLEEN

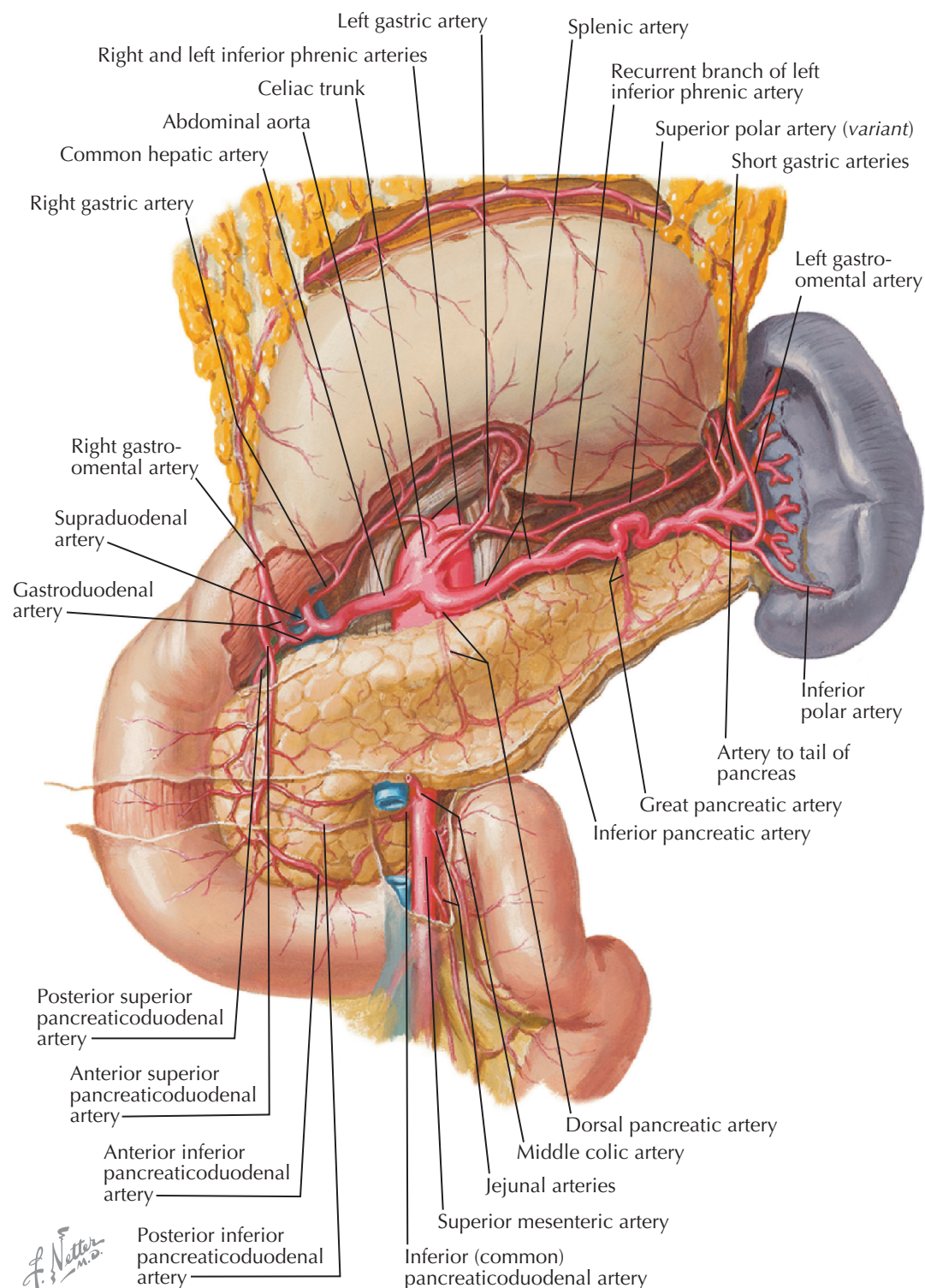
BLOOD SUPPLY OF STOMACH AND DUODENUM (Continued)

accessory left hepatic is an additive vessel that supplies a region of the left lobe of the liver (either the superior or inferior area of the lateral segment) not supplied by the incomplete celiac left hepatic. From the functional point of view, none of the hepatic arteries is ever “accessory” because every hepatic artery supplies a definite region of the liver. In view of prevalent anatomic variations, every gastric resection should be preceded by an exploratory examination to determine what type of left gastric artery is present, for severance of a left hepatic derived from the left gastric results in ischemia and fatal necrosis (7th to 16th day) of the left lobe of the liver, as repeatedly evidenced in postmortem examinations. Quite frequently, the left gastric gives off an accessory left inferior phrenic and, in some instances, the left inferior phrenic itself.

The celiac trunk may be incomplete when the right or left hepatic arteries arise from some other source. The common hepatic artery may arise in its entirety from the superior mesenteric artery (C); the superior mesenteric artery may provide the right hepatic artery in its entirety, also supplying blood to the gallbladder (D); and the superior mesenteric artery may supply an accessory right hepatic artery, which may or may not supply the gallbladder (E). The common hepatic artery may also branch very proximally, giving off an early right and left hepatic arteries while the right hepatic and gastroduodenal arteries branch from each other further to the right (F). The left lobe of the liver may also receive an accessory left hepatic artery from the right hepatic artery (G), or the right hepatic artery may cross anterior to the hepatic duct before entering the substance of the liver (H).

Invariably, the right gastric artery is much smaller (2 mm) than the left gastric (4 to 5 mm), with which it anastomoses. On occasion (8%) it gives off the supraduodenal or a spray of twigs to the first part of the duodenum. Predominantly, the gastroduodenal artery arises from the common hepatic (75%), but, in some instances, especially with a split celiac trunk, it may arise from the left hepatic (10%), right hepatic (7%), replaced hepatic trunk from the superior mesenteric or aorta (3.5%), or even directly from the celiac or superior mesenteric artery (2.5%). These atypical origins are correlated with the mode of branching of the celiac artery, for the common hepatic may divide only into the gastroduodenal and right hepatic (leaving the left hepatic to be replaced from the left gastric) or into the gastroduodenal and left hepatic with replacement of the right hepatic from the superior mesenteric. Typical branches of the gastroduodenal are (1) the posterior superior pancreaticoduodenal (90%); (2) the anterior superior pancreaticoduodenal; and (3) the right gastro-omental. Inconstant branches are (1) the right gastric (8%); (2) the supraduodenal (25%); (3) the transverse pancreatic (10%); (4) a cystic artery, either the superficial branch or the entire cystic (3%); (5) an accessory right hepatic; and (6) the middle colic or an accessory middle colic (rarely).

The relatively large posterior superior pancreaticoduodenal artery (1 to 3 mm in width) forms an arcade on the back of the head of the pancreas, with branches to the duodenum. In many instances (10%), the artery



arises from a source other than the gastroduodenal and, when it arises from the latter, it does so as its uppermost collateral branch and not as an end branch. The right gastro-omental artery is considerably larger than the left gastro-omental and, in its course, extends far beyond the midline of the greater curvature of the stomach, where it anastomoses with the left gastro-omental artery. Of great surgical import is the fact that, in many instances (10%), this anastomosis is not grossly visible, it being absent or reduced to small arterial twigs that dwindle

to nothing before the two meet. The infra-gastric omental arc, formed by the right and left gastro-omental arteries, gives off a large pyloric branch and then a variable number of ascending gastric and descending omental or anterior omental branches. The omental branches descend between the two anterior layers of the great omentum. The short ones anastomose with neighboring vessels, and the long ones proceed to the distal free edge of the great omentum, where they turn upward to become the posterior omental arteries. Many

BLOOD SUPPLY OF STOMACH AND DUODENUM (Continued)

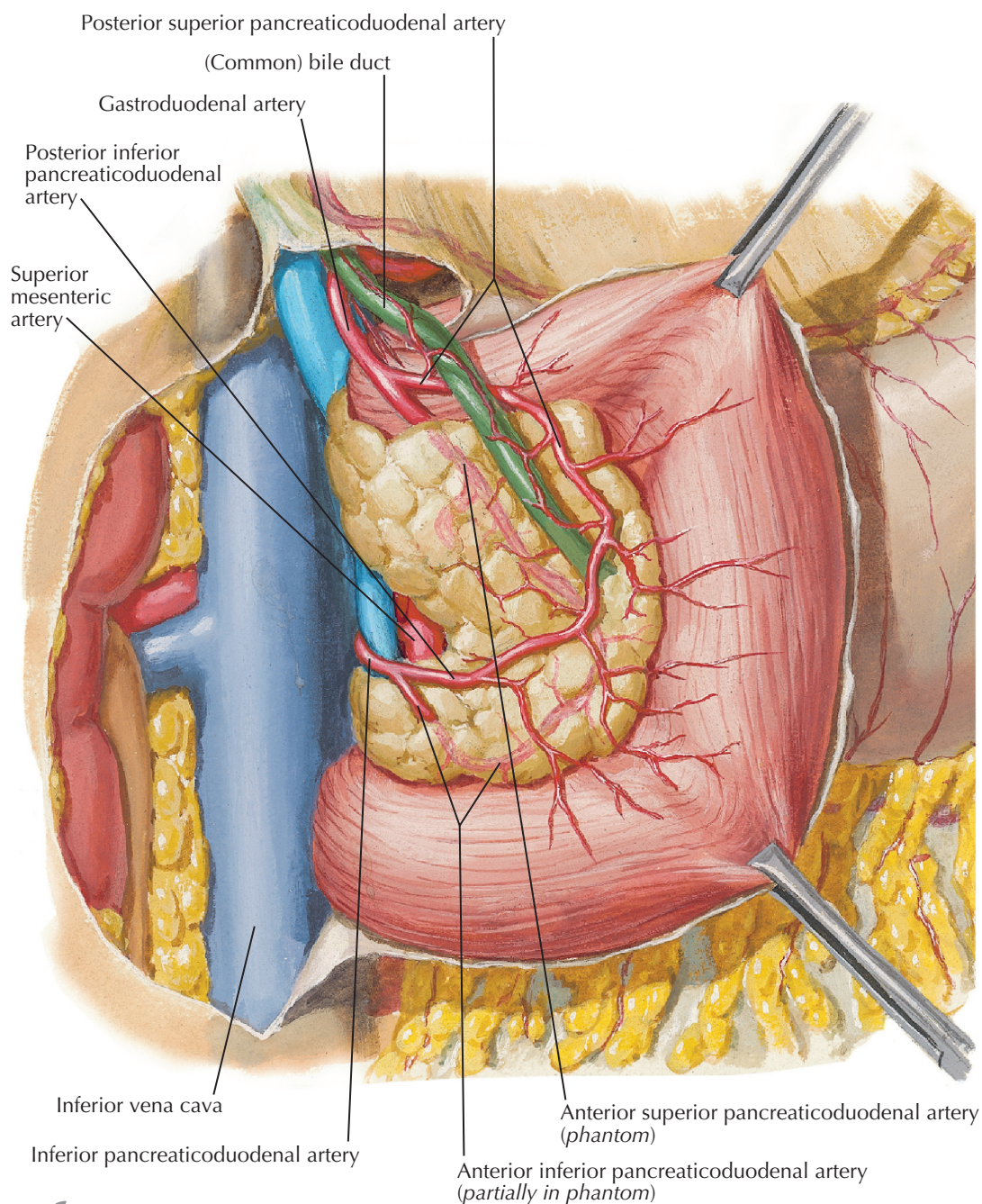
of these join the large omental arc situated in the posterior layer of the great omentum below the transverse colon. The arc is usually formed by the right omental (first branch of the right gastroepiploic) and left omental, a branch of the left gastroepiploic. Slender arteries ascend from the arc and anastomose with similar branches (posterior omentals) given off from the middle colic or left colic and from the transverse pancreatic coursing along the inferior surface of the pancreas. The ultimate and penultimate branches of the posterior omental arteries anastomose with the vasa recta of the middle colic but, apparently, are not of sufficient caliber to take over the blood supply if the middle colic has been rendered functionless. Aberrations of the right gastroepiploic are (1) an origin from the superior mesenteric (1.5%) or with the middle colic and superior pancreaticoduodenal (1%); (2) anastomoses with the middle colic, via a large vessel (1%); and (3) an origin from a gastroduodenal derived from the superior mesenteric.

Usually, the left gastroepiploic arises from the distal end of the splenic artery (75%) or from one of its splenic branches (25%) near its terminus. It may be replaced by two to three vessels, the main artery coming from the splenic trunk and the others from an inferior splenic polar artery. Branches of the left gastroepiploic are (1) short fundic branches (two to four); (2) a variable number of ascending short gastric arteries; (3) several short and long descending omental branches, some of which communicate with similar branches from the right gastroepiploic artery; (4) pancreatic rami to the tail of the pancreas, one of which, when large, is termed the artery to the tail of the pancreas; (5) an inferior splenic polar artery; and (6) the left omental artery, which descends in the great omentum to form the left limb of the omental arc, the right limb being formed by the right omental artery from the right gastroepiploic or transverse pancreatic artery.

The blood supply of the duodenum and head of the pancreas is one of the most variant in the body and, surgically considered, one of the most difficult to manipulate. The first inch of the duodenum is a critical transition zone. Paucity or insufficiency of its blood supply has repeatedly been correlated causatively with the tendency of ulcers to perforate the superior part of the duodenum just beyond the pylorus. Typically, the superior, anterior, and posterior surfaces of the first inch of the duodenum are supplied by the supraduodenal artery, which may be derived from either of two nearby arteries, the posterior superior pancreaticoduodenal artery or gastroduodenal and, in the remaining cases, from the right gastric, hepatic, or right hepatic. The supraduodenal artery frequently communicates with branches of the right gastric, gastroduodenal, and anterior and posterior superior pancreaticoduodenal arteries. The remaining portions of the duodenum are supplied by branches from two pancreaticoduodenal arcades, one anterior and the other posterior to the head of the pancreas. It is by virtue of these two arcades that the duodenum is the only section of the gut that has a double blood supply, one to its anterior surface and one to its posterior surface.

The anterior pancreaticoduodenal arcade is formed by the *anterior superior pancreaticoduodenal artery*, the smaller of the two end branches of the gastroduodenal artery. After making a loop of a half circle or less on the

ARTERIES OF DUODENUM AND HEAD OF PANCREAS



anterior surface of the pancreas, medial to the groove between the pancreas and duodenum, it sinks into the pancreas, turns to the left, and ascends, and upon reaching the posterior surface of the head of the pancreas, joins the *anterior inferior pancreaticoduodenal artery*, a branch from the *superior mesenteric artery*. The arcade gives off 8 to 10 relatively large branches to the anterior surface of all three portions of the duodenum and, in many instances, 1 to 3 branches to the first part of the jejunum; they reach the jejunum by passing deep to the

superior mesenteric artery. The arc also supplies numerous pancreatic branches, some of which are arranged in arcade fashion and anastomose with branches given off by the dorsal pancreatic artery, derived from the first part of the splenic or hepatic artery.

The *posterior pancreaticoduodenal arcade* is made by the posterior superior pancreaticoduodenal artery, which is the first branch of the gastroduodenal given off by the latter above the duodenum above the upper border of

BLOOD SUPPLY OF STOMACH AND DUODENUM (Continued)

the head of the pancreas, where it may be hidden by connective tissue. In about 10% of cases, it has a decidedly different origin, being derived from the hepatic (4%), right hepatic (2%), aberrant right hepatic from the superior mesenteric (3%), or dorsal pancreatic (1%). After its typical origin from the gastroduodenal, the artery (1 to 3 mm in width) descends for 1 cm or more on the left side of the common bile duct and then, after crossing the latter anteriorly, descends for several centimeters along its right side before swinging to the left and downward to form the posterior arcade. The major portion of the U- or V-shaped posterior arcade lies posterior to the head of the pancreas, at a level superior to that of the anterior arcade. It comes into full view when the duodenum is mobilized and turned forward to expose its posterior surface. It is covered by a fold of connective tissue sufficiently thin that its branches can be seen. It is accompanied by a venous arcade that lies superficial to the arterial arcade and that empties directly into the portal vein. The arcade crosses the intrapancreatic part of the common bile duct (to which it supplies blood) posteriorly. Ultimately, the posterior superior pancreaticoduodenal artery unites with the inferior pancreaticoduodenal artery derived from the superior mesenteric at a higher level than that of the anterior arcade (40%), or it anastomoses with a posterior branch of a common inferior pancreaticoduodenal, the latter receiving both the anterior and posterior arcades (60%). The main branches, arising from the posterior pancreaticoduodenal arcade, are (1) several descending branches (two to three) to the first part of the duodenum, one of which may be the supraduodenal; (2) duodenal branches to the posterior surfaces of the descending, transverse, and ascending duodenum; (3) small pancreatic branches that are far less numerous and are shorter than those of the anterior arcade; (4) ascending branches (one or more) to the supraduodenal portion of the common bile duct; and (5) a cystic artery (entire or its superficial branch), which, in about 4% of cases, stems from the first part of the posterior superior pancreaticoduodenal or at its site of origin from the gastroduodenal.

In the majority of instances, the anterior and posterior pancreaticoduodenal arcades have a variant anatomic structure, in the sense that the arcades may be double, triple, or even quadruple. When multiple arcades are present, it is the outer arcade near the duodenum that usually supplies the latter with its branches, whereas the inner arcades supply only pancreatic branches and ultimately become united with other branches of the celiac trunk.

With every duodenal resection, three important vascular arrangements must be borne in mind:

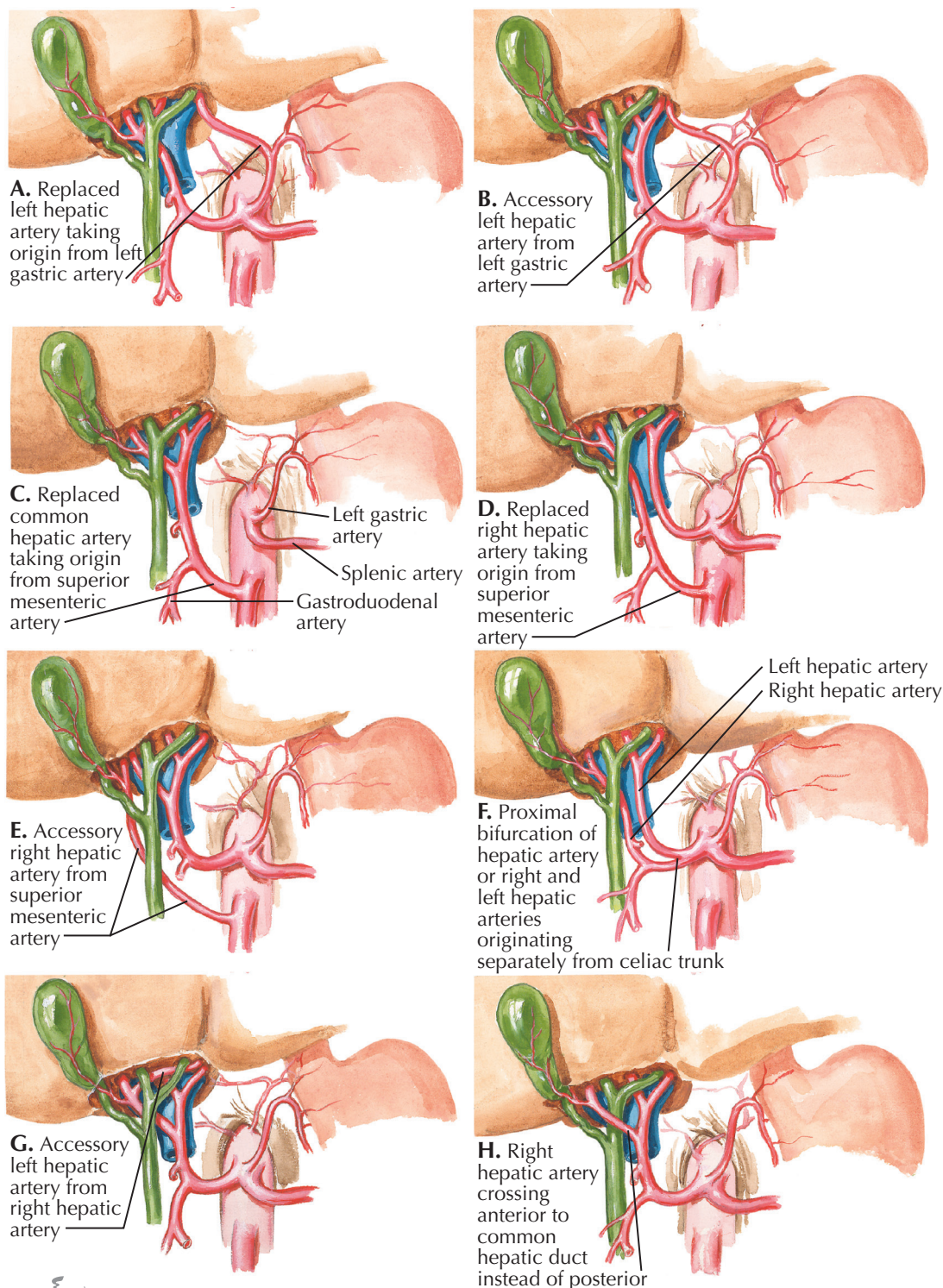
1. The entire blood supply of the duodenum and head of the pancreas may be completely dissociated from the superior mesenteric. This occurs when an aberrant right hepatic from the superior mesenteric, coursing behind the head of the pancreas, gives off one or two inferior pancreaticoduodenal arteries to receive the anterior or posterior pancreaticoduodenal arcade (or both).
2. The anterior or posterior pancreaticoduodenal arcade (or both) often ends via one or more

inferior pancreaticoduodenal arteries derived from the left side of the superior mesenteric or from its first, second, or third jejunal branch, a fact to be explored in every gastrojejunostomy, lest the blood supply of the duodenum be impaired and rendered insufficient for viability of that section of the gut.

3. In resections of the duodenum, extreme care should be taken to maintain an adequate blood

supply to the anterior and posterior surfaces of the stumps. The duodenal branches from the pancreaticoduodenal arcades are end arteries, and if these are ligated, the suture lines pass through ischemic parts that may become necrotic and break. This can result in "blowout" of the duodenal stump; such an event has repeatedly been fatal, excessive devascularization of the stump being the direct cause of the fatal issue.

HEPATIC ARTERY VARIATIONS



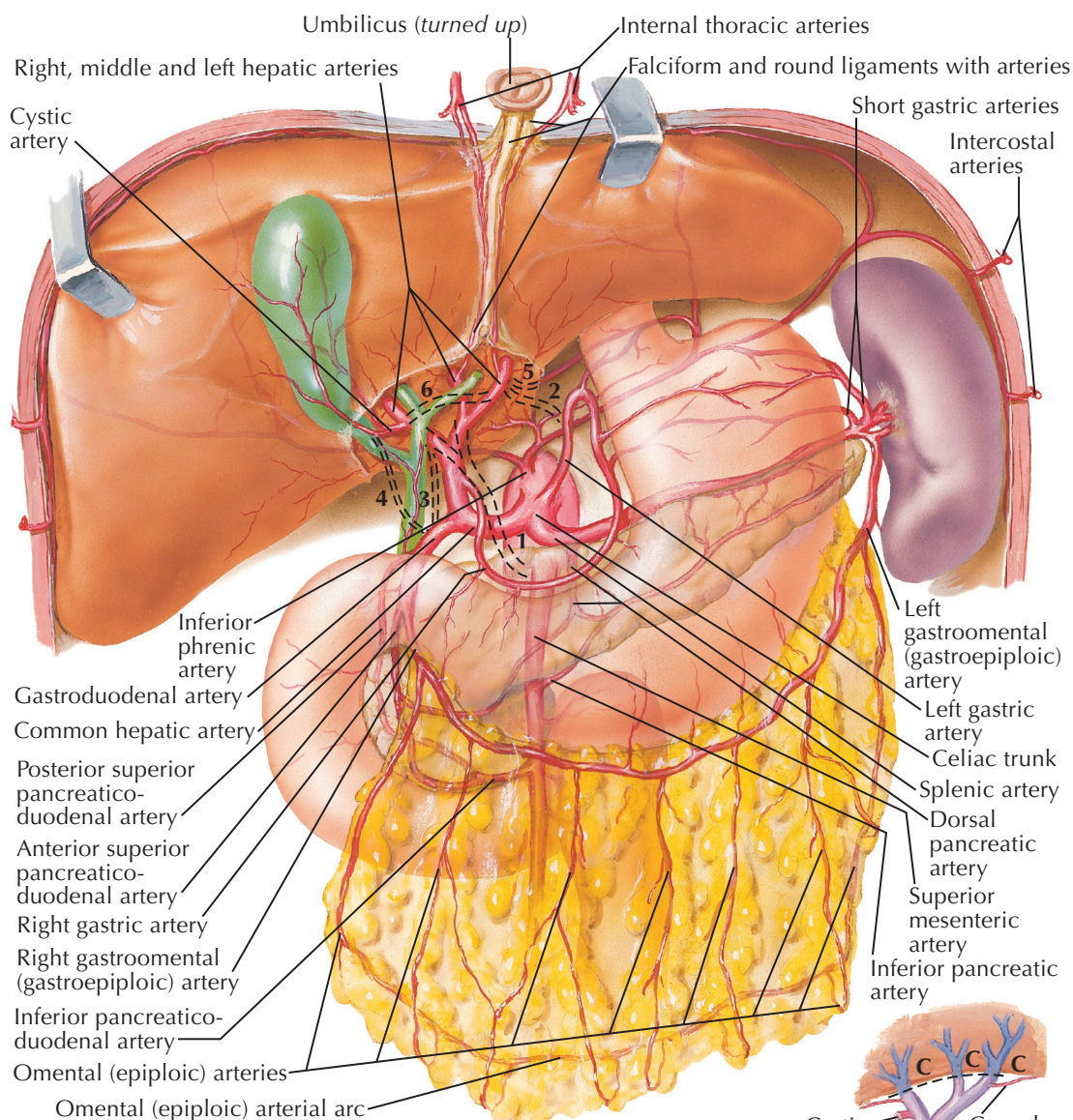
F. Netter M.D.

COLLATERAL CIRCULATION OF UPPER ABDOMINAL ORGANS

No other region in the body presents more diversified collateral pathways of blood supply than the foregut organs, the stomach, duodenum, pancreas, spleen, liver, and gallbladder. Because of the multiplicity of its blood vessels and the loose arrangement of its connective tissue, the greater omentum is exceptionally well adapted as a terrain of compensatory circulation, especially for the liver and spleen, when either the hepatic or splenic artery is occluded. The stomach may receive its blood supply from 6 primary and 6 secondary sources; the pancreas from the hepatic, splenic, and superior mesenteric; the liver from 3 primary sources (celiac, superior mesenteric, and left gastric) and, secondarily from communications with at least 23 other arterial pathways. In view of the relational anatomy of the splenic artery, it is quite obvious that most of the collateral pathways to the upper abdominal organs can be initiated via this vessel and its branches and completed through communications established by the gastroduodenal and superior mesenteric arteries.

The most important collateral pathways in the upper abdominal organs are the following:

1. Arcus arteriosus ventriculi inferior. This infragastric omental pathway is made by the right and left gastroomental arteries as they anastomose along the greater curvature of the stomach. The arc gives off ascending gastric and descending omental arteries.
2. Arcus arteriosus ventriculi superior. This supragastric pathway with branches to both surfaces of the stomach is made by the right and left gastric arteries anastomosing along the lesser curvature. Branches of the right gastric may unite with branches from the gastroduodenal, supraduodenal, posterior superior pancreaticoduodenal, or right gastroomental arteries. Branches of the left gastric artery may anastomose with the short gastric arteries from the splenic terminals, left gastroomental, branches from the recurrent cardioesophageal branch of the left inferior phrenic, or branches of an accessory left hepatic, derived from the left gastric.
3. Arcus epiploicus magnus. This omental pathway is situated in the posterior layer of the great omentum inferior to the transverse colon. Its right limb is made by the right omental artery from the right gastroomental artery, and its left limb by the left omental artery from the left gastroomental artery. Arteries involved in this collateral route include hepatic, gastroduodenal, right gastroomental, right omental, left omental, left gastroomental, and inferior terminal branches of the splenic.
4. Circulus transpancreaticus longus. This important collateral pathway is effected by connections between the dorsal pancreatic artery and splenic artery. The dorsal pancreatic may communicate with the first part of the splenic, hepatic, celiac, or superior mesenteric, depending on which artery gives rise to the dorsal pancreatic. At the tail end of the pancreas, it communicates with the splenic terminals via the great pancreatic artery, inferior pancreatic artery, and artery to the tail of the pancreas, and at the head of the pancreas with the gastroduodenal, superior pancreaticoduodenal, or right gastroomental arteries.
5. Circulus hepatogastricus. This is a derivative of the primitive, embryonic arched anastomosis between the left gastric and the left hepatic arteries.



Accessory or replaced arteries

1. Right or common hepatic
2. Left hepatic
3. Right hepatic
4. Cystic

Anastomoses of corresponding arteries

5. Inferior phrenic/left gastric ↔ left hepatic
6. Right ↔ left hepatic

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ies. In the adult the arc may persist in its entirety; the upper half may give rise to an accessory left gastric, and the lower half to an "accessory" left hepatic from the left gastric artery.

6. Circulus hepatolienalis. Here an aberrant right hepatic or the entire common hepatic artery, arising from the superior mesenteric artery, may communicate with the splenic artery via a branch of the dorsal pancreatic or gastroduodenal, inferior pancreatic, or artery to the tail of the pancreas.
7. Circulus celiacomesentericus. Through the inferior pancreaticoduodenal, blood may be routed through the anterior and posterior pancreatico-

Effects of hepatic artery obstruction

- A. Zone of relative safety
- B. Zone of questionable effects
- C. Zone of inevitable infarction

duodenal arcades to enter the gastroduodenal artery, from which, via the right and left gastroomental arteries, it reaches the splenic, or, via the common hepatic, it reaches the celiac.

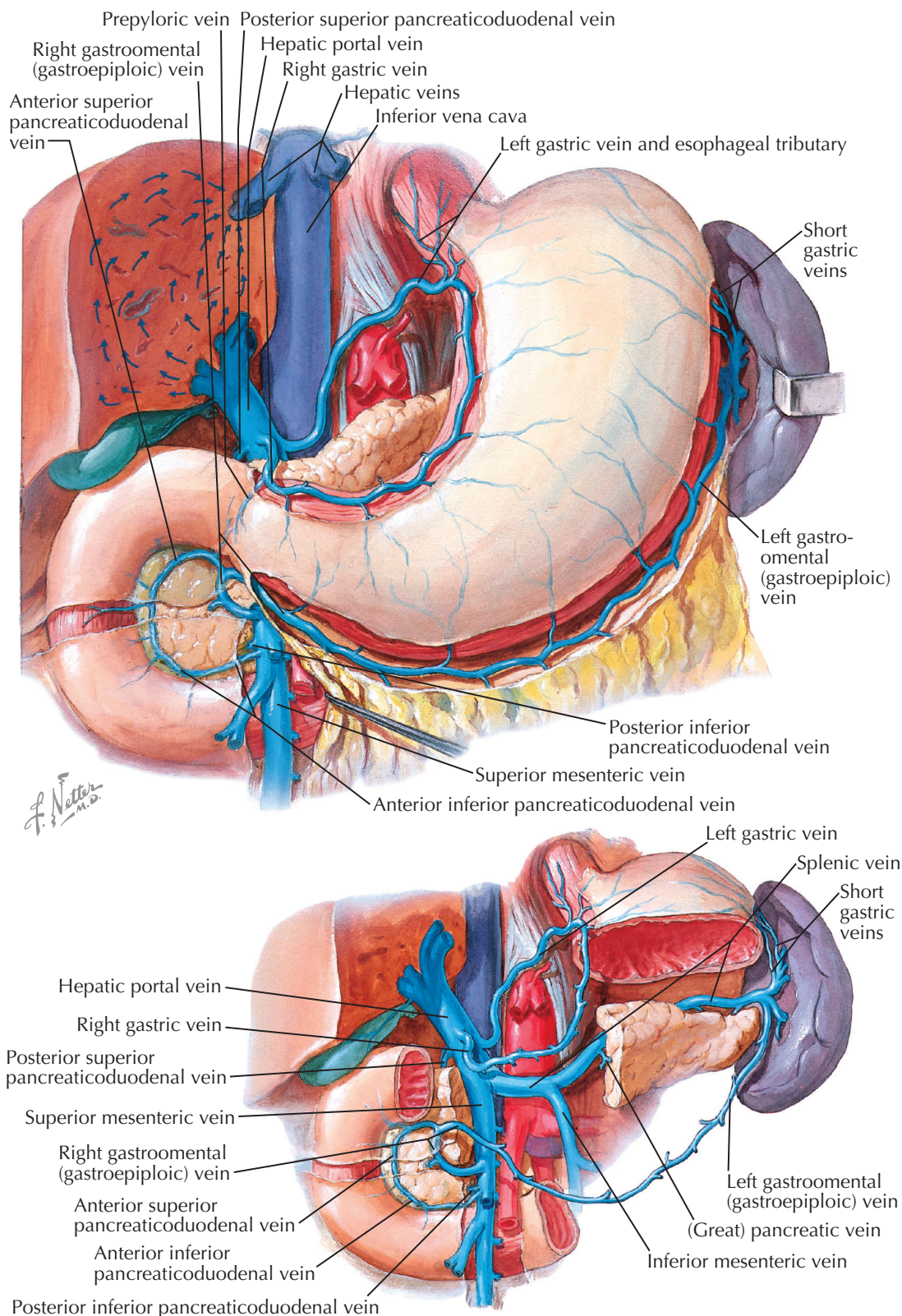
8. Circulus gastrolienophrenicus. This connection may exist (1) via a communication between the short gastric arteries from the splenic terminals and the recurrent cardioesophageal branches of the left inferior phrenic or (2) via a communication between the latter and the cardioesophageal branches given off by the left gastric, its aberrant left hepatic branch, or an accessory left gastric from the left hepatic.

VENOUS DRAINAGE OF STOMACH AND DUODENUM

Venous blood from the stomach and duodenum, along with that from the pancreas and spleen and that of the remaining portion of the intestinal tract (except the anal canal), is conveyed to the liver by the *portal vein*. The portal vein resembles a tree, in that its roots (capillaries) ramify in the intestinal tract, whereas its branches (sinusoids, capillaries) arborize in the liver. From its point of formation to its division within the liver into right and left branches, the portal vein measures from 8 to 10 cm in length and from 8 to 14 mm in width. Typically, the portal vein is formed by the union of the *superior mesenteric vein* with the *splenic vein*, posterior to the neck of the pancreas. Its tributaries show many variations that are extremely important in operative procedures. The *inferior mesenteric vein* opens most commonly into the splenic vein (38%) but, in many instances, drains into the junction point of the superior mesenteric and splenic veins (32%) or into the superior mesenteric vein (29%). Occasionally, it bifurcates, opening into both veins.

The *left gastric vein* accompanies the left gastric artery and runs from right to left along the lesser curvature of the stomach, at the cardioesophageal end of which it receives esophageal branches. It may empty into the junction point of the superior mesenteric and splenic veins (58%), *portal vein* (24%), or *splenic vein* (16%). The *right gastric vein* accompanies the right gastric artery from left to right, receives tributaries from both surfaces of the superior part of the stomach, and, usually, opens directly into the lower part of the portal vein (75%). Frequently, it enters the superior mesenteric (22%) and occasionally the *right gastroepiploic* or *inferior pancreaticoduodenal veins*. In some instances, it has a common termination with the left gastric vein or is not identifiable. The *left gastroepiploic vein* receives branches from the lower anterior and posterior surfaces of the stomach, greater omentum, and pancreas. It usually opens into the distal part of the splenic vein and, less frequently, into an inferior branch of the splenic vein. *Short gastric veins* arising from the fundus and cardiac regions of the stomach join the splenic terminals or the splenic branches of the left gastroepiploic veins, or they enter the splenic vein directly. The *right gastroepiploic vein* courses along the greater curvature of the stomach, where it receives branches from its anterior and posterior surfaces and from the greater omentum. Usually, it terminates in the superior mesenteric vein (83%) just before that vessel joins the portal vein. Occasionally, it enters the first part of the splenic or portal vein (2%).

The pancreaticoduodenal veins run alongside the anterior and posterior arterial pancreaticoduodenal arcades. The *anterior and posterior inferior pancreaticoduodenal veins* fuse into a single vein that usually joins the superior mesenteric vein below the entry of the right



gastroepiploic vein. Frequently, the posterior arcade empties directly into the portal vein. The *posterior superior pancreaticoduodenal vein* typically drains to the portal vein. The *cystic vein*, formed by superficial and deep tributaries from the gallbladder, may enter the portal vein directly or its right branch, or drive to the liver directly. The majority of pancreatic venous branches, arising from the body and tail of the pancreas, join the splenic vein along its course, whereas others terminate

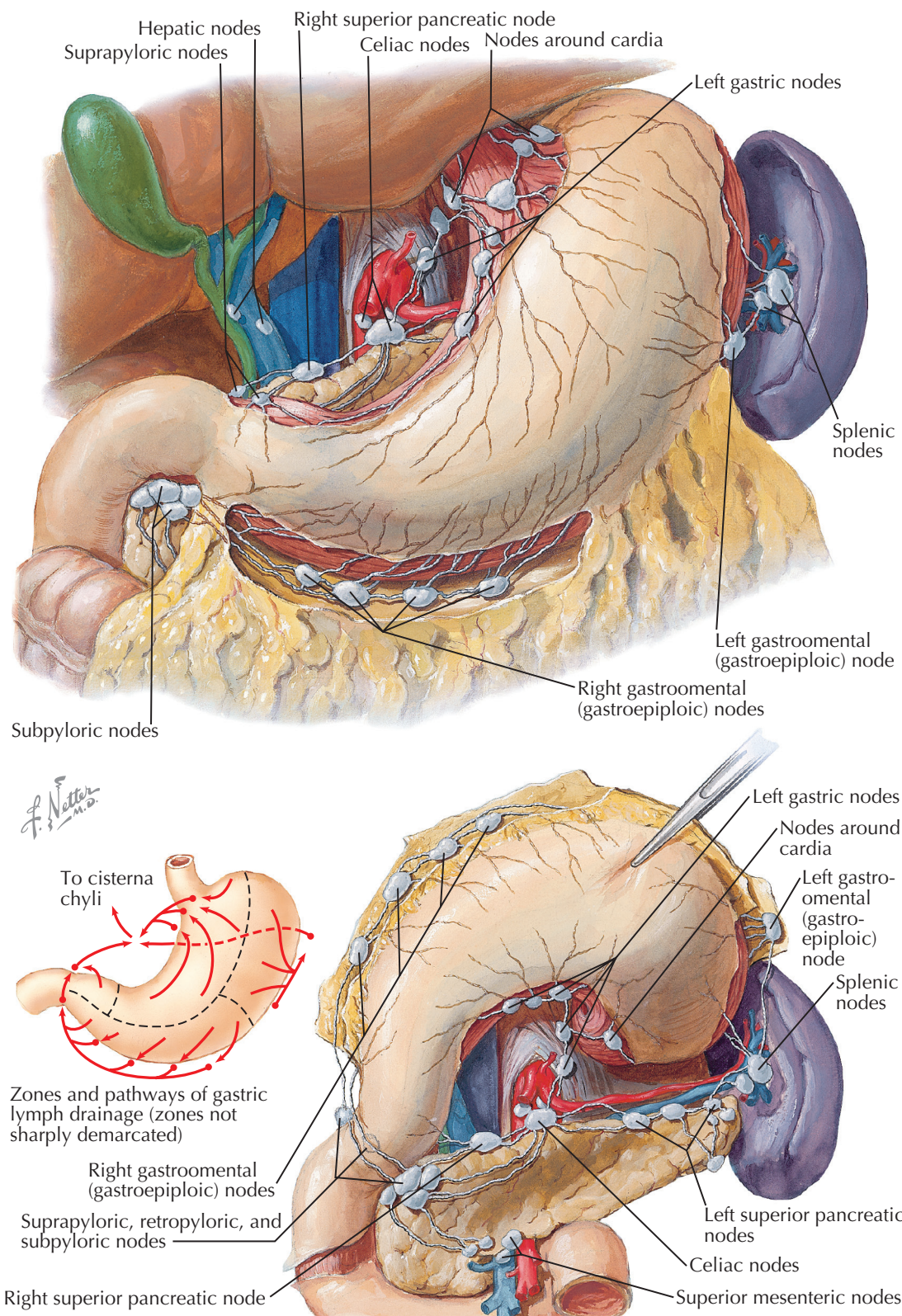
in the upper part of the superior or inferior mesenteric vein or left gastroepiploic vein. The left inferior phrenic vein receives a tributary from the cardioesophageal region of the stomach and, usually, enters the suprarenal vein but, in some instances, joins the renal vein.

Because all larger vessels of the portal system are devoid of valves, collateral venous circulation in portal obstruction is readily effected via communications with the caval system.

LYMPHATIC DRAINAGE OF STOMACH

The lymph from the gastric wall collects in the lymphatic vessels, which form a dense subperitoneal plexus on the anterior and posterior surfaces of the stomach. The lymph flows in the direction of the greater and lesser curvatures, where the first regional lymph nodes are situated. On the upper half of the lesser curvature (i.e., the portion near the cardia) are the *left gastric lymph nodes*, which are connected with the *lymph nodes around the cardia*. Progressing around the lesser curvature may be a few *right gastric lymph nodes*. Superior, inferior, and posterior to the pylorus are located the *suprapyloric*, *subpyloric*, and *retropyloric lymph nodes*, respectively. On the greater curvature, following the trunk of the right gastroepiploic artery and distributed in a chainlike fashion within the gastrocolic ligament, are the *right gastroepiploic lymph nodes*. From these nodes the lymph flows to the right toward the subpyloric nodes, which are situated anterior to the head of the pancreas, inferior to the pylorus and the first part of the duodenum. There are a few smaller *left gastroepiploic lymph nodes* in the part of the greater curvature nearest to the spleen.

For purposes of simplification, a distinction can be made between four different drainage areas into which the gastric lymph flows, although, in point of fact, these areas cannot be so rigidly separated. The lymph from the upper left anterior and posterior walls of the stomach (excluding the far left fundus and body) drains through the left gastric nodes and nodes around the cardia. From there, lymphatic fluid follows the left gastric artery and the coronary vein toward the vascular bed of the celiac artery. Included in this system are additional *left gastric lymph nodes* near the left crus of the diaphragm. The pyloric segment of the stomach, in the region of the lesser curvature, discharges its lymphatic fluid into the *right superior pancreatic lymph nodes*, partly directly and partly indirectly, via the small suprapyloric nodes. The lymphatic fluid from the left region of the fundus (i.e., adjacent to the spleen) flows along lymphatic vessels within the gastrosplenic ligament. Some of these lymphatics lead directly to the *left superior pancreatic lymph nodes*, and others move indirectly via the small *left gastroepiploic lymph nodes* and via the *splenic nodes* lying within the hilus of the spleen. Lymph from the distal portion of the inferior stomach along the right greater curvature and inferior pyloric region collects in the right gastroepiploic lymph nodes. From here, the lymph flows to the subpyloric nodes, which lie anterior to the head of the pancreas, partly posterior and partly inferior to the pylorus. Leading to these nodes are also a few lymphatics from that part of the greater curvature that is immediately adjacent to the pylorus. From the subpyloric lymph nodes, which are also connected with the superior mesenteric nodes by way of *prepancreatic lymphatics*, the lymph flows to the



right superior pancreatic nodes through lymphatics situated behind the pylorus and duodenal bulb.

From the left gastric nodes, right superior pancreatic nodes, and left superior pancreatic nodes, lymphatic fluid leads to the *celiac lymph nodes*, situated superior to the pancreas at the base of the celiac arterial trunk and its branches. From the celiac lymph nodes, lymph flows through the gastrointestinal lymphatic trunk to reach the *thoracic duct*, in the initial segment of which is

generally a more or less pronounced expansion, called the *cisterna chyli*.

The thoracic duct projects superiorly through the posterior and superior mediastinum to open into the angle formed by the left subclavian and left jugular veins, often receiving the left subclavian lymphatic trunk prior to insertion. In cases of gastric tumor, palpable metastases may sometimes develop in the *left supraclavicular (Virchow) lymph nodes* in this area.

AUTONOMIC INNERVATION OF STOMACH AND DUODENUM

INNERVATION OF STOMACH AND DUODENUM

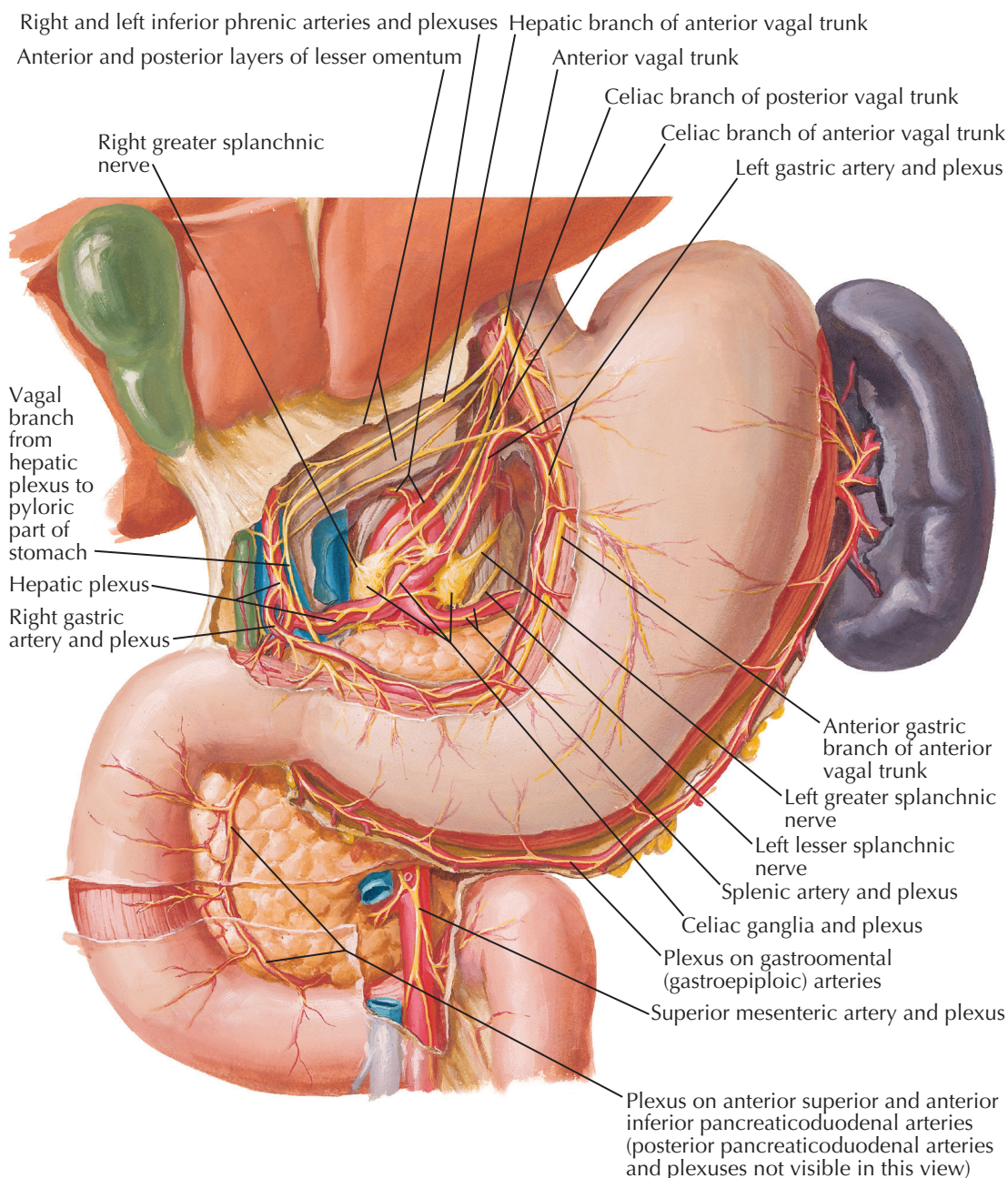
The stomach and duodenum are innervated by the visceral efferent sympathetic and parasympathetic nerves, along which run visceral afferent fibers.

The **SYMPATHETIC** supply to the stomach emerges in the anterior spinal nerve roots as presynaptic axons projecting from cells within the *intermediolateral cell column* of the spinal cord, particularly from the 5th to the 9th or 10th thoracic segments. They are carried from the *spinal nerves* in *white rami communicans* that pass to the adjacent *sympathetic ganglia* located along the length of the *sympathetic trunk*. The sympathetic axons that will supply the stomach pass through the thoracic vertebrae as the *thoracic splanchnic nerves*, which pass through the diaphragm posteriorly to reach *celiac ganglia*. Generally, these axons will form synapses with postsynaptic nerve cells in the celiac and *superior mesenteric ganglia*. The postsynaptic axons of these cells are conveyed to the stomach and duodenum in the *celiac plexus* and the *superior mesenteric plexus*. We will concentrate on the former, as it is the primary nerve supply to the stomach and proximal duodenum. The axons of the celiac plexus adhere to the walls of the arteries that arise from the celiac arterial trunk; they may be referred to as the *hepatic plexus*, *splenic plexus*, or *left gastric plexus*, depending upon which artery they follow. The sympathetic axons of each plexus run alongside presynaptic parasympathetic axons and visceral afferent axons.

Subsidiary plexuses from the hepatic arterial plexus are continued along the right gastric and gastroduodenal arteries and from the latter along the *right gastroomental* and *anterior and posterior superior pancreaticoduodenal arteries*. The splenic arterial plexus sends offshoots along the short gastric and left gastroomental arteries.

The *left gastric plexus* consists of one to four branches that accompany the artery and supply twigs to the cardiac region of the stomach and communicate with offshoots from the left phrenic plexus. Other filaments follow the artery along the lesser curvature of the stomach between the layers of the lesser omentum to supply adjacent parts of the stomach. They communicate profusely with the *right gastric plexus* and with gastric branches of the vagus. The nearby *phrenic plexuses* assist in supplying the cardiac end of the stomach. A filament from the *right plexus* sometimes turns to the left and passes to the region of the cardiac orifice, whereas the left phrenic plexus supplies a constant twig to the cardiac orifice. A delicate branch from the left phrenic nerve (not illustrated) supplies the cardia.

The *splenic plexus* gives off subsidiary nerve plexuses around its pancreatic, short gastric, and left gastroomental branches, and these supply the structures



indicated by their names. A filament may curve upward to supply the fundus of the stomach.

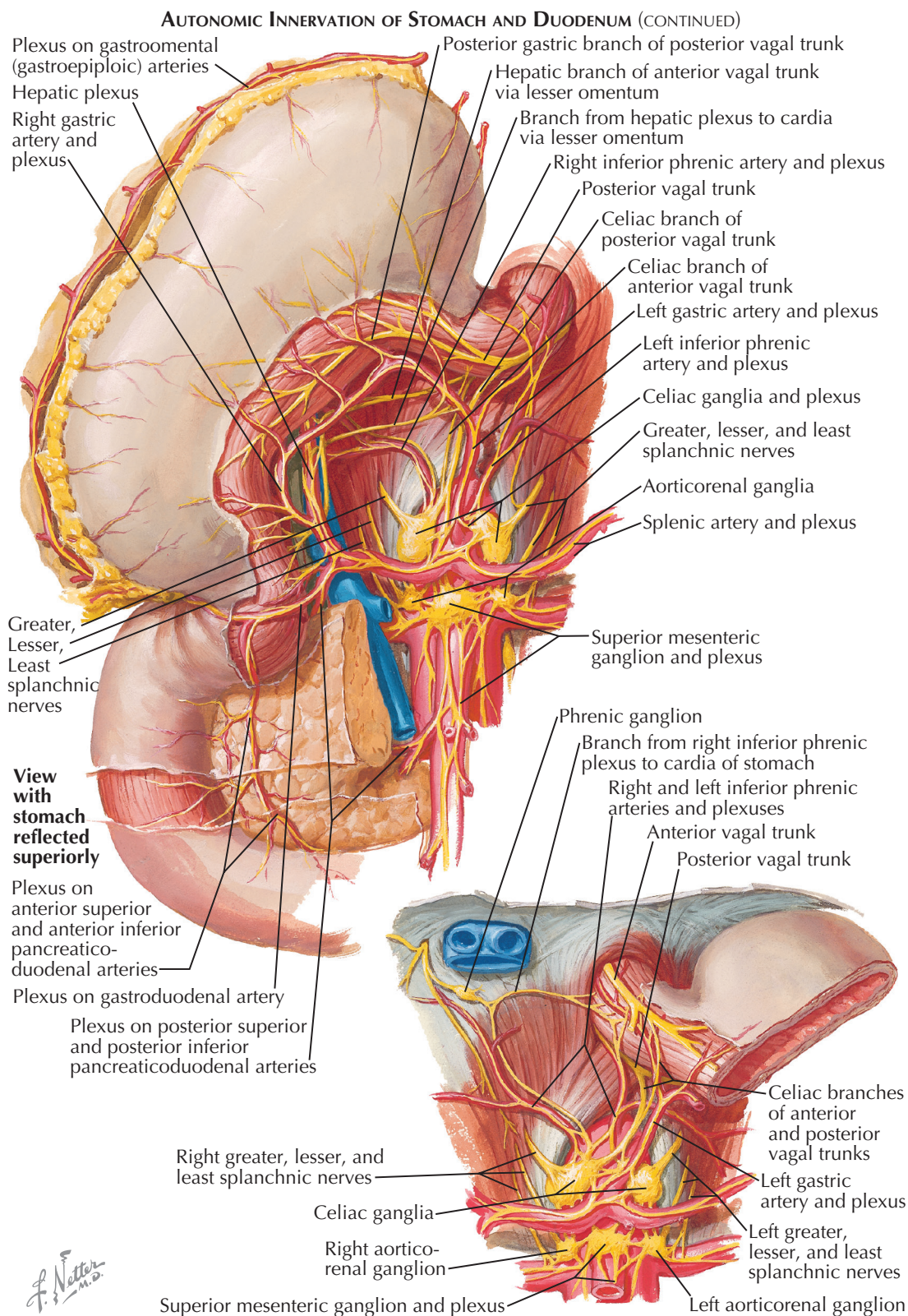
The *hepatic plexus* gives off subsidiary plexuses along all its branches. These, following the right gastric artery, supply the pyloric region, and the gastroduodenal plexus accompanies the artery between the first part of the duodenum and the head of the pancreas, supplying fibers to both structures and to the adjacent parts of the common bile duct. When the artery divides into its anterior superior pancreaticoduodenal and right

gastroomental branches, the nerves also subdivide and are distributed to the second part of the duodenum, the terminations of the common bile and pancreatic ducts, the head of the pancreas, and the parts of the stomach. The part of the hepatic plexus lying in the free margin of the lesser omentum gives off one or more (hepatogastric) branches that pass to the left between the layers of the lesser omentum to the cardiac end and lesser curvature of the stomach; they unite with and reinforce the left gastric plexus.

INNERVATION OF STOMACH AND DUODENUM (Continued)

The *superior mesenteric ganglion* is primarily involved in supplying postsynaptic axons to the midgut organs. It does supply the distal duodenum by means of axons that follow the anterior and posterior inferior pancreaticoduodenal arteries to reach the duodenum and pancreatic head.

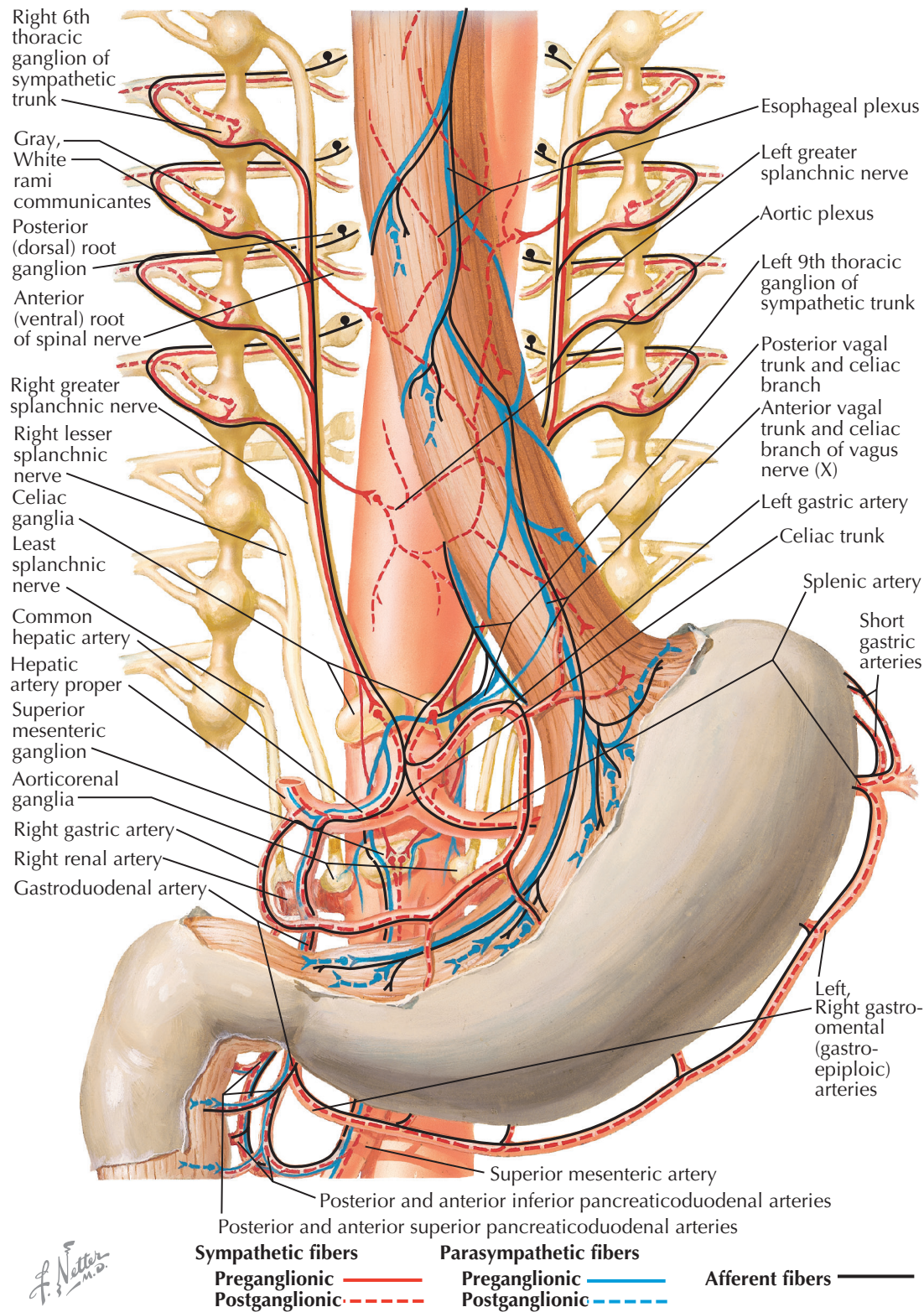
The **PARASYMPATHETIC SUPPLY** of the stomach and duodenum arises in the dorsal vagal motor nucleus in the floor of the fourth ventricle. The dorsal vagal motor nuclei contribute presynaptic parasympathetic axons to the left and right *vagus nerves*, which leave the jugular foramen to innervate thoracic and abdominopelvic organs. We will ignore the activity of the vagus nerves in the thorax other than to mention that the left and right vagus nerves closely associate with the esophagus and interweave to produce the *anterior and posterior vagal trunks*, which pierce the diaphragm alongside the esophagus to enter the abdominal cavity. The anterior vagal trunk travels on the anterior aspect of the stomach and across the *hepatogastric ligament* to innervate some of the liver and gallbladder. Frequently, one branch, the *greater anterior gastric nerve*, is larger than the others. The various gastric branches can be traced for some distance beneath the serous coat before they sink into



the muscle coats, and although they communicate with neighboring gastric nerves, a true anterior gastric plexus in the accepted sense of the term does not usually exist. The pyloric branches (not illustrated) arise from the anterior vagal trunk or from the greater anterior gastric nerve and run to the right between the layers of the lesser omentum before turning inferiorly through or close to the hepatic plexus to reach the pyloric antrum, pylorus, and proximal part of the duodenum.

Small celiac branches run alongside the left gastric artery to the celiac plexus, often uniting with corresponding branches of the posterior vagal trunk. The posterior vagal trunk moves further posteriorly from the esophagus to run into the nearby celiac ganglion. In contrast to the presynaptic sympathetic axons entering the celiac ganglion, the presynaptic parasympathetic axons do not synapse there but instead pass through the ganglion to enter the *celiac plexus*. From

AUTONOMIC INNervation OF STOMACH AND DUODENUM: SCHEMA



INNERVATION OF STOMACH AND DUODENUM *(Continued)*

there these axons, alongside the postsynaptic sympathetic axons from the celiac ganglion and viscerosensory axons, travel along branches of the celiac trunk, the hepatic, splenic, and left gastric plexuses, to reach the foregut organs. When these presynaptic parasympathetic axons reach the target organs, they synapse with postsynaptic parasympathetic nerve cell bodies located within the organs' walls.

Viscerosensory activity related to the stomach and duodenum is divided into two categories, visceral pain and normal visceral reflexive stimuli. The stomach is insensitive to ordinary tactile, painful, and thermal stimuli, although it responds strongly to tension, ischemia, and chemical irritations as visceral pain. Visceral pain fibers travel in a retrograde fashion along the sympathetic innervation of the stomach; therefore, visceral pain axons traveling along the left gastric, right gastric, left gastro-omental, or right gastro-omental plexuses would eventually reach the celiac ganglion. Without synapsing, such an axon would continue along the greater thoracic splanchnic nerves, through the sympathetic chain ganglia, and then through the white rami communicans, anterior ramus, and spinal nerve. At this time, being afferent, the axon would travel along the posterior root to reach the spinal cord. Prior to

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reaching the spinal cord, the axon encounters (but does not synapse within) its nerve cell body. The nerve cell bodies of these viscerosensory axons are located in the posterior (dorsal) root ganglia. Because these nerve cells are pseudounipolar, their axon extends from the target tissue to reach the cell body but also proximally to reach the posterior gray horn of the spinal cord.

Nonpainful, reflexive stimuli from the stomach travel in a retrograde manner along its parasympathetic inner-

vation. Because all foregut organs receive their presynaptic parasympathetic innervation via the vagus nerves, reflexive visceral afferents from the stomach ascend along the vagus nerve to reach the brainstem and then project to the inferior aspect of the solitary nucleus. The cell bodies for these axons are located in the *inferior vagal ganglion*, which is located near the point at which the vagus nerves exit from the right and left jugular foramina.

NORMAL GASTRIC NEUROMUSCULAR PHYSIOLOGY

Normal gastric physiology is best described in terms of its fasting patterns and the responses of the stomach in response to food intake (the fed response).

FASTING GASTRIC MOTILITY

Fasting gastric contractile patterns are characterized by a cyclic motor phenomenon called the *migrating motor complex*. In healthy people in the fasting state, it occurs approximately once every 90 minutes, most prominently at night. The fasting state generally starts approximately 4 hours after meal ingestion, when the stomach has completely emptied a meal. The fasting contractile patterns consist of a period of quiescence (phase I), a period of intermittent pressure activity (phase II), and an activity front, during which the stomach and small intestine contract at their highest frequency (phase III). During phase III of the migrating motor complex, contraction frequencies reach 3 a minute in the stomach and 11 or 12 a minute in the proximal small intestine. This *interdigestive contraction wave* (*intestinal housekeeper*) progresses down the stomach and small intestine and serves to help empty the stomach of indigestible solids and transport them down the small intestine into the colon. These contractile pressures, especially in the fasting period, are generally recorded with antroduodenal manometry, a catheter recording pressures from the stomach (primarily antral region) and the small intestine (primarily duodenum).

GASTRIC RESPONSES TO MEAL INGESTION

Normally with solid food ingestion, the upper stomach relaxes (*gastric accommodation*), allowing the proximal stomach to accommodate the ingested meal. This is followed by a progressively tonic contraction of the fundus to deliver food into the distal stomach. Within the antrum, regular peristaltic contractions grind down solid food so that it can be passed down the stomach toward the pylorus. The pyloric sphincter opens in a coordinated fashion with antral contractions, allowing the smaller particle size (food chyme) to empty from the stomach into the small intestine. Larger food particles are retropulsed back toward the body of the stomach, where they are ground down further; this process is repeated until the particles are small enough to empty through the pylorus.

GASTRIC ACCOMMODATION

Gastric accommodation is a postprandial, vagally mediated reflex resulting in reduced gastric tone, primarily in the proximal stomach, that occurs with eating a meal. Gastric accommodation provides a reservoir for ingested foods without a significant increase in intragastric pressure.

The accommodation reflex has two principal components. *Receptive relaxation* occurs within seconds of eating and is triggered by both oropharyngeal and gastric stimulation. This response involves relaxation of both the lower esophageal sphincter and proximal stomach. *Adaptive relaxation* is a slower process triggered by gastric or duodenal distention and is perhaps also modified by specific nutrients. The accommodation reflex is vagally mediated and represents the



Normally with solid food ingestion, the upper stomach relaxes, allowing the proximal stomach to accommodate the ingested meal. This is followed by a progressively tonic contraction to deliver food into the distal stomach. Within the antrum, regular peristaltic contractions grind down solid food so that it can be passed toward the pyloric sphincter which opens, allowing the food to empty from the stomach.

balance between the cholinergic excitatory drive and nonadrenergic noncholinergic inhibitory input. The afferent signal is generated by activation of stretch-sensitive mechanoreceptors in the stomach wall, osmoreceptors, and chemoreceptors in the stomach and duodenum. The efferent nonadrenergic noncholinergic signal involves nitric oxide as the principal neurotransmitter. A role for vasoactive intestinal polypeptide has also been suggested.

GASTRIC EMPTYING OF A MEAL

Normal gastric emptying reflects a coordinated effort between the fundus, antrum, pyloric sphincter, and duodenum. Coordination of these fundic-antral-pyloric-duodenal motor events is carefully regulated and governed by (1) gastrointestinal electrical activity through the interstitial cells of Cajal, (2) neural connectivity through enteric nerves in the enteric nervous system, and (3) vagal efferent nerves from the central nervous system (CNS). Feedback from nutrients and the volume in the stomach and small bowel affects the process of gastric emptying and is conveyed through

local enteric sensory nerves, vagal afferent nerves, and hormones.

Fundic and antral smooth muscle contractions are primarily cholinergically mediated. Rhythmic antral contractions, generally at 3 cycles per minute, triturate large food particles into an appropriate size for intestinal digestion. The rate of these contractions is governed by the electrical pacemaker of the stomach and the interstitial cells of Cajal.

Pyloric sphincter relaxation, often synchronized with antral contractions, allows smaller food particles and chyme to pass out of the stomach into the duodenum. Pyloric relaxation is mediated through release of inhibitory nerves, especially nitric oxide and, possibly, vasoactive intestinal polypeptide.

Solid foods and liquids leave the stomach at different rates. Liquids empty at an exponential rate because their emptying depends primarily on the gastroduodenal pressure gradient and less on pyloric opening. Solids are initially retained selectively within the stomach until particles have been triturated to a size smaller than 2 mm, at which point they can be emptied at a linear rate from the stomach.

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MECHANISM OF GASTRIC ACID SECRETION

The stomach has three anatomic regions, the fundus, body, and antrum. It is functionally divided into two glandular regions, the oxyntic and pyloric mucosae. The *oxyntic gland mucosa* contains parietal cells (that produce gastric acid (hydrogen chloride [HCl]) producing) and forms 80% of the fundus and body. The *pyloric gland mucosa* contains G cells and forms 20% of the antrum. Chief cells predominate at the base and secrete pepsinogen and leptin. The distinct neuroendocrine cell types and their physiologic functions are the (1) enterochromaffin cells, which contain atrial natriuretic peptide, somatostatin, serotonin, and adrenomedullin; (2) enterochromaffin-like cells, which contain histamine; (3) D cells, which contain somatostatin; and (4) cells that contain ghrelin and obestatin.

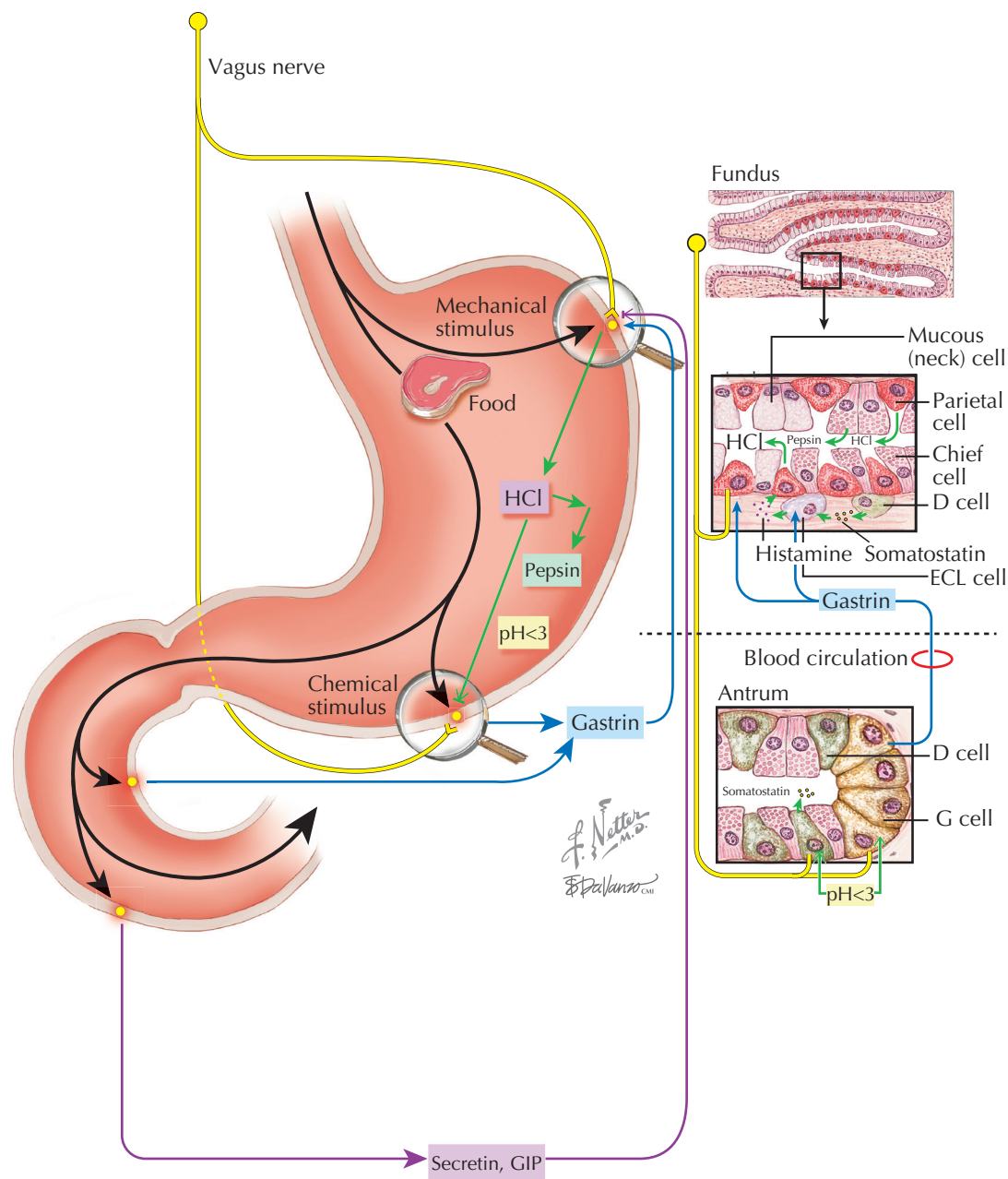
The physiologic stimulation of acid secretion is divided into three phases, the cephalic, gastric, and intestinal phases.

1. The cephalic phase is activated by the thought, taste, smell, and sight of food. Swallowing is mediated mostly by cholinergic/vagal mechanisms. The conditioned (psychic) secretion (described by Pavlov) is the principal component of the cephalic phase; hence, dogs were conditioned to associate the ringing of a bell with a meal. Anticipation of food is a powerful trigger for increasing gastric secretions. Other upregulated systems include the pancreas and gallbladder.
2. The gastric phase is due to the chemical effects of food and distention of the stomach mediated by gastrin with a marked increase in gastric blood flow supplying the metabolic requirements of the actively secreting cell types.
3. As the meal moves out of the stomach into the duodenum, the intestinal phase occurs. The buffering capacity of the lumen is reduced and the pH begins to fall. This feedback response involves several endocrine and paracrine factors, including gastric inhibitory polypeptide and cholecystokinin (CCK).

Physiologic secretion enhancers are vagal activation, food, and gastric distention. Parietal cells secrete HCl at a concentration of approximately 160 mmol, or pH 0.8, produced from the hydration of carbon dioxide to form H^+ and HCO_3^- , catalyzed by carbonic anhydrase. The acid secretory process requires functional receptors, signaling pathways, channels, transporters, and acid-secreting pumps ($H^+/K^+-ATPase$).

Basal acid output is approximately 10% of the maximal acid output of the stimulated parietal cell. There is diurnal variation of basal acid levels, with night levels being higher than day levels.

The parietal cell contains another inhibitory receptor for prostaglandin E_2 (PGE_2) which inhibits gastric acid secretion by decreasing intracellular cyclic adenosine monophosphate levels and gastrin secretion and stimulates somatostatin secretion. Gastric acid facilitates digestion of proteins and absorption of calcium, iron, and vitamin B_{12} . It also suppresses growth of bacteria, preventing enteric infections and small intestinal bacterial overgrowth. Low levels of acid are related to chronic atrophic gastritis and precancerous gastric conditions. Gastric acid secretion from parietal cells is regulated by overlapping pathways that include endocrine (gastrin), paracrine (histamine and somatostatin), neural (acetylcholine), and probably autocrine (trans-



forming growth factor alpha) factors. The source of gastric acid secretion is the parietal cell, located in the glands of the fundic mucosa. Its basolateral membrane contains receptors for histamine, gastrin, and acetylcholine; potentiated secretion may occur when all are present simultaneously. In the resting state, parietal cells are filled with secretory vesicles that form channels that drain to the apical lumen. The secretory membrane lining these structures contains the hydrogen-potassium-ATPase acid-secreting pump. This pump is always active, but it exists in a short-circuited state in resting vesicles because of inactive exchange. With stimulation, this pathway becomes active, and hydrogen-potassium exchange occurs.

With ingestion of a protein meal, gastrin is released; it enhances gastric acid secretion from parietal cells through release of histamine from enterochromaffin-like cells and has a direct effect on parietal cells.

Many dietary substances are highly effective buffers. Carbohydrates and fats inhibit acid secretion, and fat

stimulates CCK and other mediators that inhibit acid secretion. Somatostatin inhibits gastric acid secretion by affecting gastrin/histamine synthesis and release. The mucosal nerves mediate the response to the cephalic phase of acid secretion and to gastric distention. Acetylcholine is the major stimulatory mediator that increases gastrin release, stimulates parietal cells, and inhibits somatostatin secretion. Other stimulatory mediators include bombesin, vasoactive intestinal peptide, and pituitary adenylate cyclase-activating polypeptide. Gastrin acts via activation of the CCK2 receptor located on parietal and enterochromaffin-like cells. Prostaglandins inhibit acid secretion and gastrin-stimulated histamine release. Gastric acid hypersecretion may be seen in chronic *Helicobacter pylori* infection, duodenal ulcers, Zollinger-Ellison gastrinoma, or mastocytosis or if an antrum is retained following partial gastrectomy. Rebound acid hypersecretion occurs once therapy with an H_2 receptor antagonist or a proton pump inhibitor has ceased for 1 month or longer.

DIGESTIVE ACTIVITY OF STOMACH

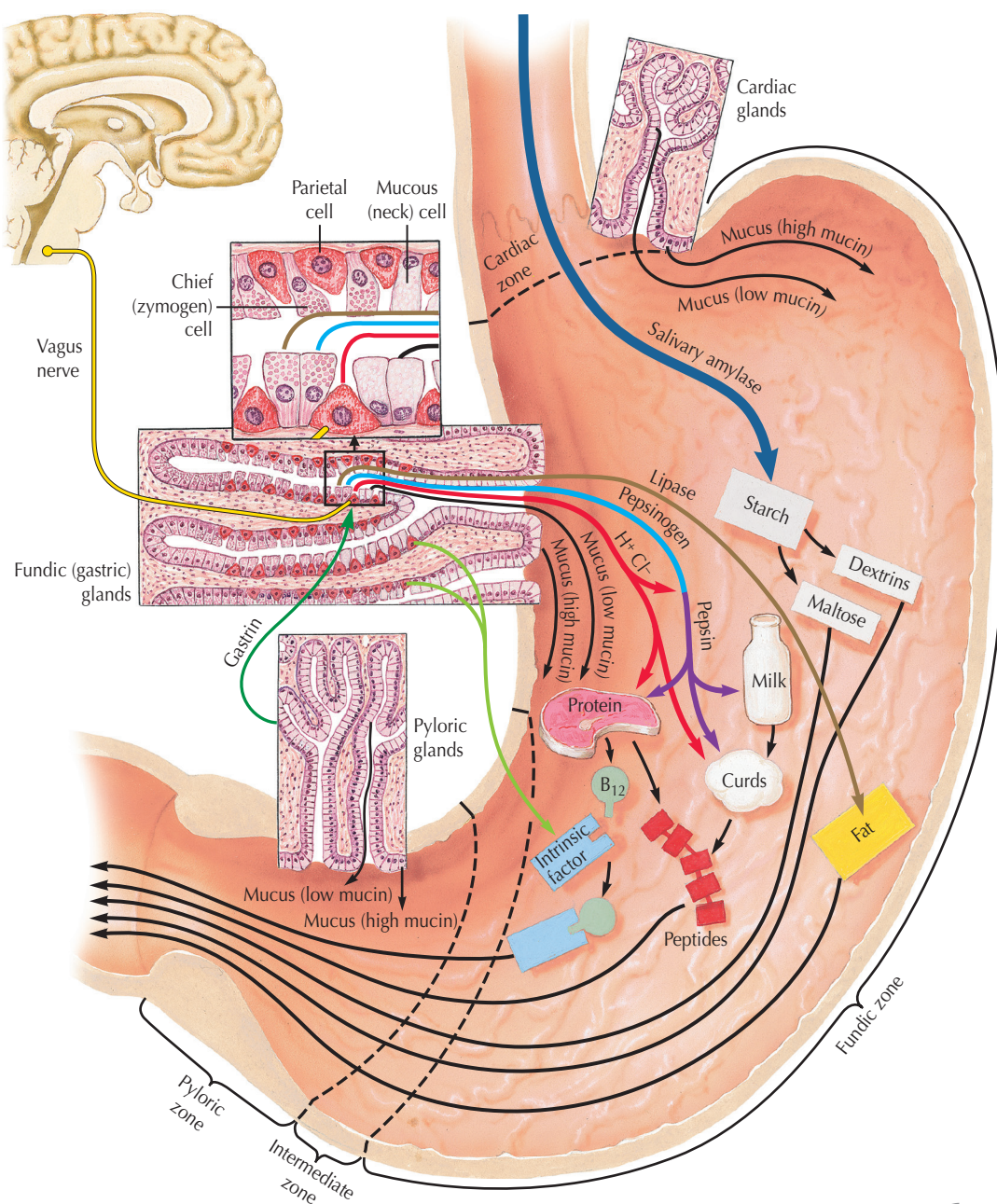
The main role of the stomach is to prepare food for digestion and absorption by the intestine. The parietal cells produce hydrochloric acid in gastric secretions. Various neural and hormonal mediators contribute to gastric function. The acid secretory process requires functional receptors, signaling pathways, channels, transporters, and acid-secreting pumps ($H^+/K^+-ATPase$). The level of acidity depends upon the relative proportions of parietal and nonparietal secretions; hence, the more rapid the rate of secretion, the higher the level of acidity.

Rebound acid hypersecretion occurs after therapy with proton pump inhibitors or H_2 receptor antagonists has ceased. Increased HCl secretion has been seen at night and with the acid secretory response to a meal. The *alkaline tide* (decrease in urinary acidity after a meal) is generally attributed to increased alkalinity of the blood resulting from the secretion of HCl . Its occurrence is influenced by the rate of formation of HCl and its absorption from the gut. Additional influencing factors include alkaline digestive secretions (mainly pancreatic), the neutralizing capacity of the food eaten, respiratory adjustments after a meal, and the diuretic effect of a meal.

Pepsin, the principal enzyme of gastric juice, is stored in the chief cells as *pepsinogen*. At a pH below 6.0, pepsinogen is converted to pepsin. The free pepsin activates the continued transformation of pepsinogen to pepsin. The chief cells are the most common cells in the gastric mucosa, found in the body, fundus, and antrum of the stomach, as well as in the duodenum. Pepsinogen is stimulated by acetylcholine, histamine, and CCK2 and inhibited by somatostatin.

Powerful stimuli for gastrin secretion include gastric juice rich in pepsin, hypoglycemia (vagal stimulus), or direct electrical stimulation of the vagus nerves. The pepsinogen of the gastric chief cells is also secreted internally into the bloodstream and appears in the urine as uropepsinogen.

As mentioned previously, gastric acid secretion is divided into cephalic, gastric, and intestinal phases. Mucus is excreted from neck cells and surface mucus



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cells in the stomach and Brunner glands after stimulation with acetylcholine, secretin, and prostaglandins. Its function is to provide a protective layer over the gastric and duodenal mucosa. Mucus slows the diffusion of acid from the lumen to the mucosa, provides lubrication for the passage of food, and maintains a near-normal pH at the mucosal surface because of its content of bicarbonate. It is dissolved by pepsin and N-acetylcysteine and easily penetrated by bile salts, ethanol, and nonsteroidal antiinflammatory drugs (NSAIDs), leading to mucosal damage. Mucosal repair is very quick and occurs through the movement of already established mature mucosal cells over the basal lamina.

Acetylcholine, histamine, endogenous nitric oxide, and PGE_2 cause vasodilation and increased gastric

blood flow; sympathetic stimulation, exogenous epinephrine, norepinephrine, and vasopressin cause vasoconstriction and decreased gastric blood flow.

Parietal cells synthesize and secrete intrinsic factor, which plays a key role in absorption of vitamin B_{12} in the terminal ileum. NSAIDs inhibit the cyclooxygenase (COX) enzyme in the prostaglandin production pathway and cause damage to the gastric mucosa. Currently there are two isoforms, COX-1 and COX-2. The COX-1 pathway results in production of PGE_2 , and the COX-2 pathway is involved mainly in inflammatory events. The selective COX-2 inhibitors decrease inflammation without affecting PGE_2 production. Mucosal defenses can also be affected by *H. pylori* infection.

NEUROREGULATION OF GASTRIC ACTIVITY

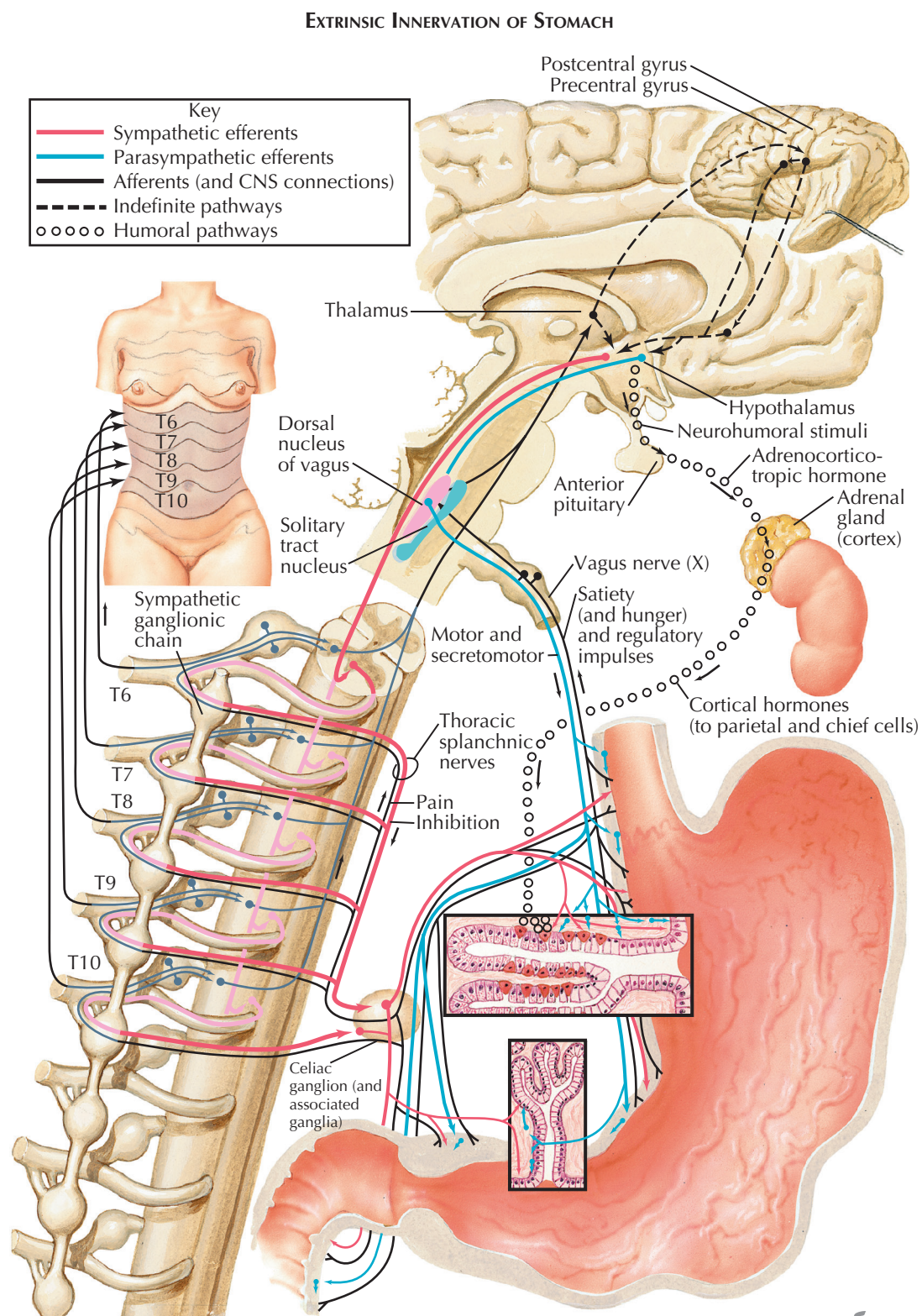
EFFERENT INNERVATION

The cortical areas that influence gastric motility and secretion are in the *posterior orbital gyrus* and the *adjacent anterior cingulate gyrus*. Connections are made, via the *medial thalamic nuclei*, with the *hypothalamus*, where fibers descend in the dorsal longitudinal fasciculus, at least as far as the *dorsal nucleus of the vagus*. Impulses from the anterior hypothalamic region act on the *cranial parasympathetic nuclei in the brainstem*, and the *posterior hypothalamus* makes connections with the neurons of the *lateral horns* of gray matter in the thoracolumbar segments of the spinal cord.

The efferent innervation of the stomach and duodenum, which governs motility and secretion, includes the vagus and sympathetic nerves. The vagus nerves, the principal means of innervation to the stomach, exert augmentative and inhibitory effects on both motility and secretion through the enteric nervous system (see below). Gastric tone, motility, and secretory activity are permanently reduced when the vagus nerves are sectioned, whereas section of the splanchnic nerve does not essentially alter the functions of the stomach. By virtue of the autonomy exercised by the intramural enteric nervous system containing the plexus and nerves, the stomach is able to function adequately after complete extrinsic denervation (i.e., after bilateral vagotomy and splanchnicotomy).

ENTERIC INNERVATION

The vagus nerves and sympathetic nerves help regulate gastric motility by synapsing on neural cell bodies and projections of the intrinsic intramural enteric nervous system. The enteric nervous system consists of a system of neurons that governs the function of the gastrointestinal system. The enteric neurons synapse on the smooth muscle to reduce or augment gastric contractions. The gastric contraction frequency is governed by the pacemaker cells in the stomach, the interstitial cells of Cajal. The neurons of the enteric nervous system are collected into two types of ganglia, the *myenteric (Auerbach) plexus*, which regulates motility, and the *submucosal (Meissner) plexus*, which regulates secretion. Myenteric plexuses are located between the inner and outer layers of the muscularis propria, and submucosal plexuses are located in the submucosa. The enteric nervous system is capable of autonomous functions, such as the coordination of reflexes; although it receives considerable innervation from the autonomic nervous system, it can



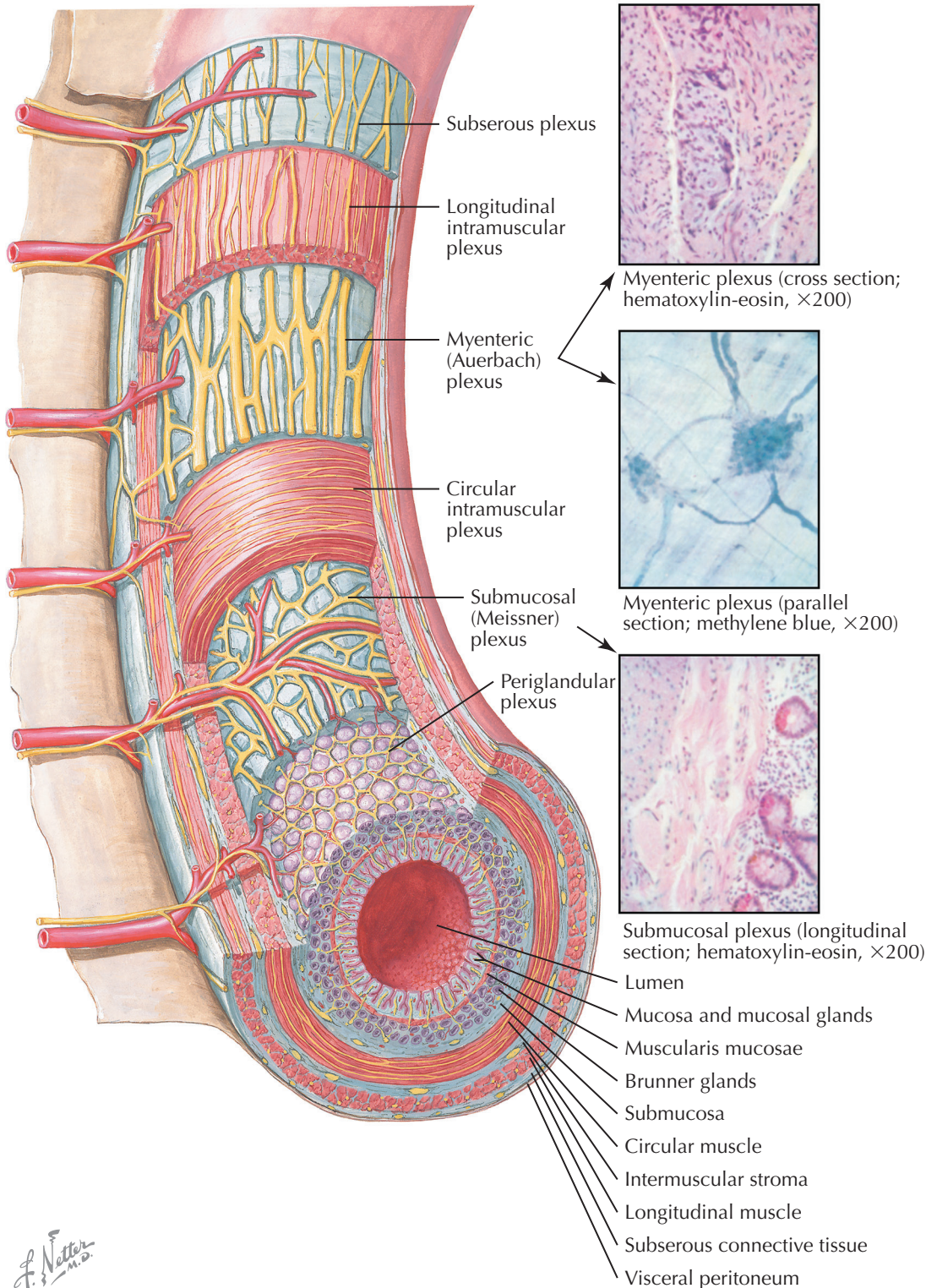
and does operate independently of the brain and spinal cord. Because the enteric nervous system has its own independent reflex activity, it has been described as a "second brain."

AFFERENT INNERVATION

The gastrointestinal tract is densely innervated to provide information on its luminal contents, processes regulating digestion and absorption. This information

is collected by intrinsic and extrinsic afferent nerves and regulates physiologic responses for homeostasis and health. In brief, sensory neurons of the enteric nervous system activate local responses. Extrinsic afferent nerves transmit sensory information to the spinal cord or brainstem for further processing and integration. In general, the extrinsic afferent innervation of the gut is conducted through the vagus nerve and spinal afferents. The cell bodies of the vagus afferents are in the nodose ganglion, and mainly project to the nucleus of the

ENTERIC NERVOUS SYSTEM



NEUROREGULATION OF GASTRIC ACTIVITY (Continued)

solitary tract. Vagovagal reflexes result in stimulation of vagal efferents in the dorsal motor nucleus of the vagus nerve. Examples of vagovagal reflexes are transient lower esophageal sphincter relaxations and meal-induced gastric accommodation.

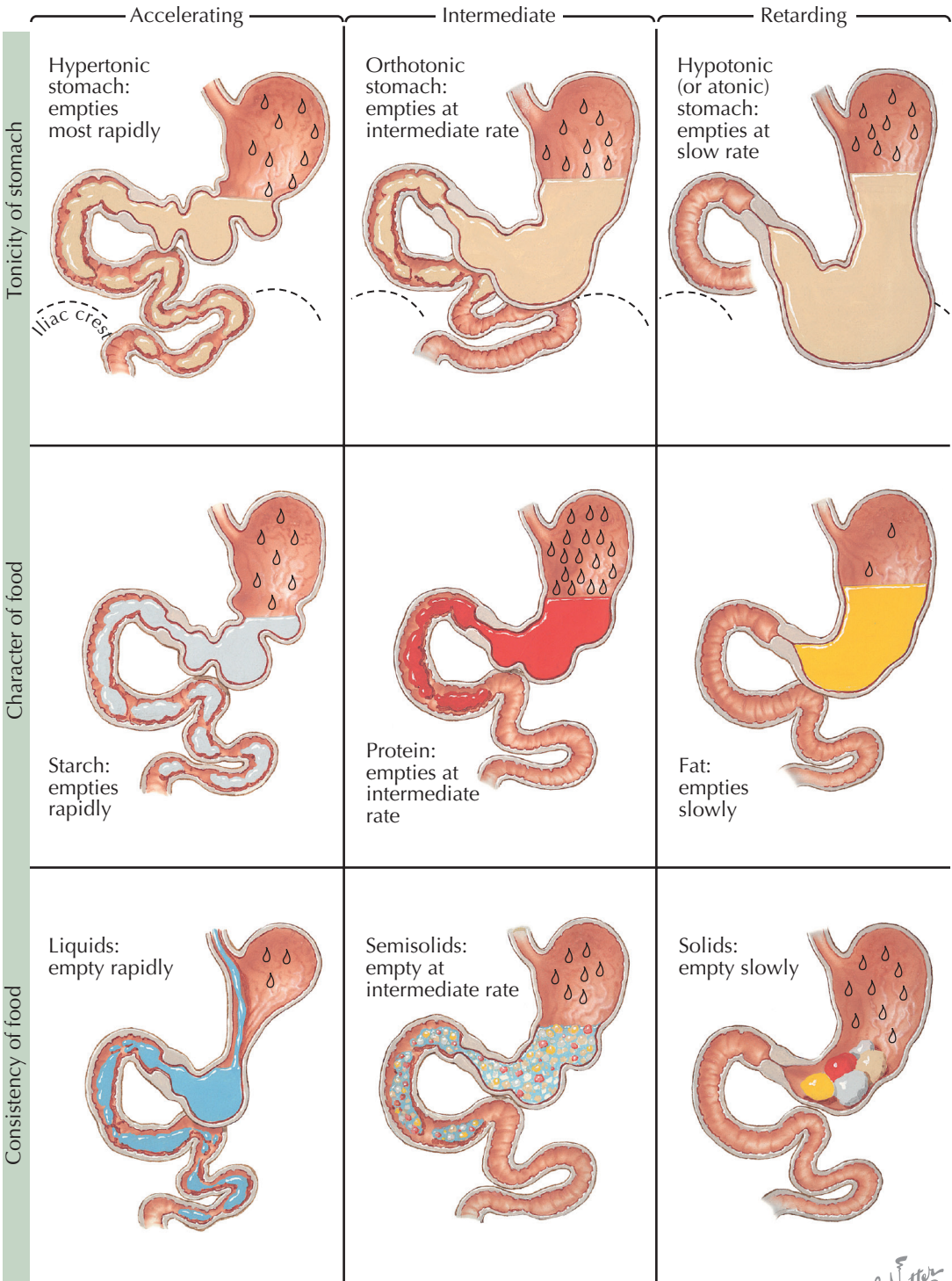
The spinal afferents have cell bodies in dorsal root ganglia. These afferents are thoracolumbar nerves (with neurons in thoracolumbar dorsal root ganglia and projections via splanchnic nerves and mesenteric/colonic/hypogastric nerves) or lumbosacral nerves (with cell bodies in lumbosacral dorsal root ganglia and projections via pelvic nerves and rectal nerves to the distal bowel), which synapse in the spinal cord and send information to the brainstem. Of note, each region of the gastrointestinal tract receives dual sensory innervation reflecting functional connectivity for the distribution of extrinsic primary afferents in these pathways.

The *afferent sensory fibers* take their course with the vagus and sympathetic nerves and mediate the visceral sensations, including nausea, hunger, and pain. Pain sensations are carried by afferent fibers accompanying the sympathetic nerves. In contrast to the somatic sensory nerves, the visceral afferents or their receptors are relatively insensitive to stimuli such as cutting or burning. The effective stimulus for visceral pain is tension transmitted to the nerve endings by strong muscular contraction, by distention, or by inflammation. Normal peristaltic movements of the stomach do not ordinarily give rise to any sensation, but forceful contractions may be perceived as a feeling of gnawing and tension or as actual pain in the abdomen, particu-

larly in the presence of an inflammatory or ulcerative process.

In addition to the discomfort that the individual locates in the involved viscus, pain may be felt which is subjectively interpreted as arising in the abdominal or thoracic wall. The *areas* to which this *referred pain* is ascribed depend upon the distribution of the afferent fibers and their course. Pain from the stomach is conveyed mainly in the afferents that run in the *sympathetic* *nerves of the 5th to 10th thoracic segments*, but the pathways may also extend as low as the 12th segment. The impulses reach the spinal cord by way of the white communicating rami and dorsal root ganglia. Within the spinal cord, the impulses are “transferred” to the neurons of the somatic sensory nerves, with the result that pain originating in the stomach may be referred to any of the somatic structures receiving their sensory supply from the 5th to 12th thoracic segments.

LOCAL FACTORS



FACTORS INFLUENCING GASTRIC ACTIVITY

Motor and secretory activities of the stomach are modified, usually simultaneously and in the same direction, by a number of factors, both local (gastric) factors and external or systemic factors. Chief among them are the following:

LOCAL (GASTRIC) FACTORS INFLUENCING GASTRIC ACTIVITY

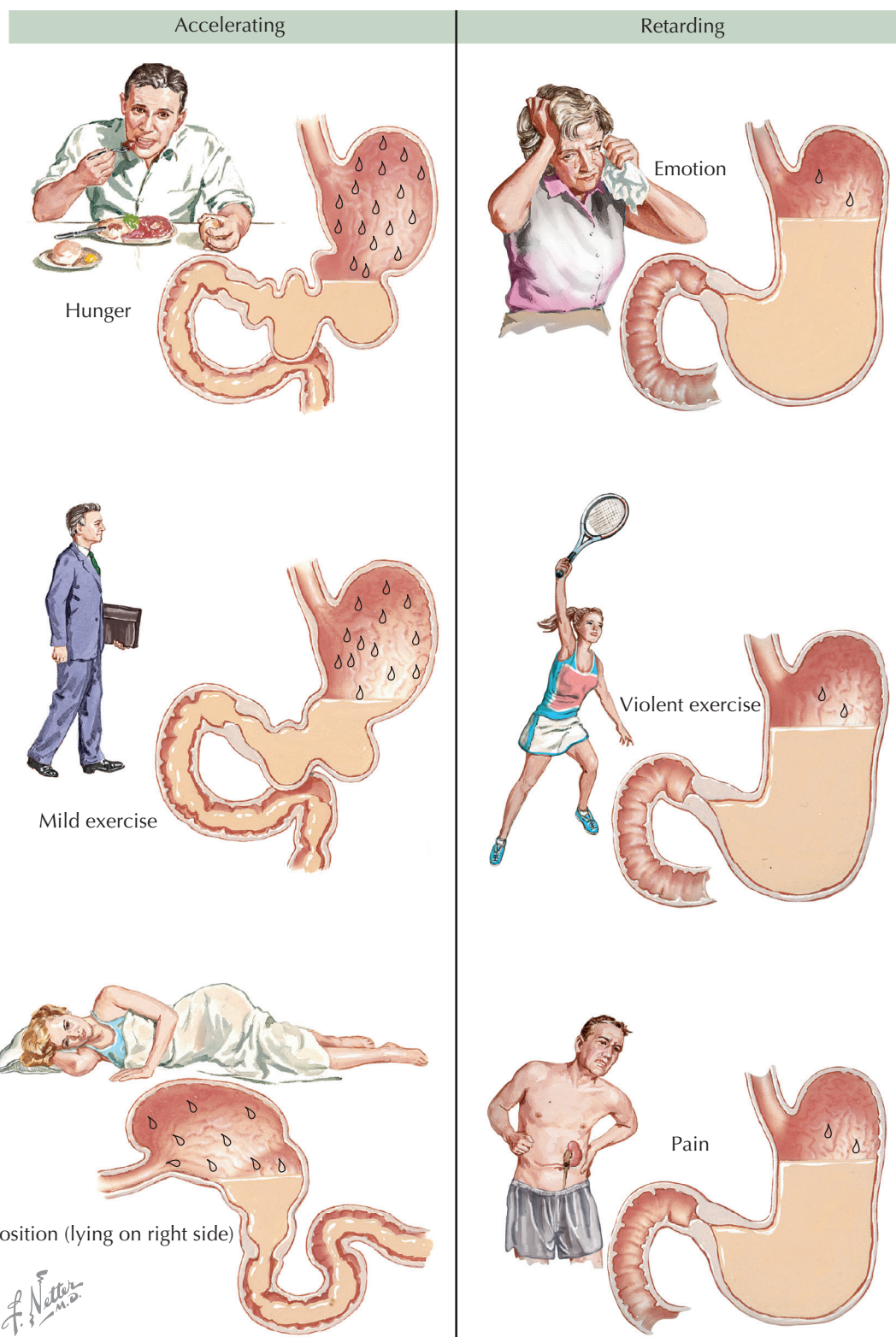
1. CHARACTER OF THE FOOD. A meal that is sufficiently *high in fat* to yield an intragastric fat content in excess of about 10% empties much more slowly and stimulates considerably less acid secretion than does a meal *predominantly of protein*. The inhibitory effect of fat on gastric secretion is not a local one but a result of the hormone, which is released systemically when fat enters the duodenum. This enterogastric inhibitory action of fat and cholecystokinin is much more effectively achieved by the ingestion of 15 to 30 mL of a vegetable oil before meals.
A meal exclusively or *mainly of starch* tends to empty more rapidly, though stimulating less secretion, than does a protein meal. Thus, other factors being equal, a person may expect to be hungry sooner after a breakfast of fruit juice, cereal, toast, and tea than after one of bacon, eggs, and milk. The amount of gastric secretion and gastric acidity is highest with the ingestion of proteins. This relationship of quantity and rate of secretion and its acid or pepsin concentration is

subject to great individual variations as well as variations in a single individual under different conditions.

2. CONSISTENCY OF THE FOOD. *Liquids*, whether ingested separately or with solid food, empty from the stomach more rapidly than do *semisolids* or *solids*. This does not apply to liquids such as milk, from which solid material is precipitated on contact with gastric juice; milk also releases CCK from its fat content. In the case of foods requiring

mastication, the consistency of the material reaching the stomach should normally be semisolid, thereby facilitating gastric secretion, digestion, and evacuation. Important exceptions to the general rule that liquids are weak stimulants of gastric secretion are (1) the broth of meat or fish, by virtue of their high secretagog content, and (2) coffee, which derives its secretory potency from its content both of caffeine and of the secretagoges formed in the roasting process.

SYSTEMIC FACTORS



FACTORS INFLUENCING GASTRIC ACTIVITY (Continued)

SYSTEMIC (EXTERNAL) FACTORS INFLUENCING GASTRIC ACTIVITY

1. **HUNGER.** A meal eaten at a time of intense hunger tends to be evacuated more rapidly than normally, apparently as the consequence of the heightened gastric tonus. Because hunger results from the depletion of body nutrient stores, it is understandable on teleologic grounds that in the hunger state, the body should have some mechanism for hastening the delivery of ingested nutrients into the intestine. Levels of the hormone ghrelin are higher when the stomach is empty and one becomes hungry, possibly signaling the time to consume a meal. Ghrelin also has prokinetic effects that accelerate gastric emptying.
2. **EXERCISE.** Mild to moderate exercise such as walking, particularly just after eating, increases gastric emptying of the meal compared with resting conditions. With strenuous exercise, gastric contractions are temporarily inhibited and gastric emptying decreases. Secretory activity does not appear to be materially influenced by exercise.
3. **POSITION.** Gastric emptying is facilitated in certain individuals when lying on the right side when the position of the body is such that the pylorus and duodenum are in a dependent position. In the supine position, gastric emptying is delayed because the gastric content pools in the dependent fundic portion. No evidence is available that secretion is affected by position. For

patients with gastrointestinal reflux symptoms, sleeping in the right recumbent position may reduce nocturnal symptoms, because delayed gastric emptying can cause reflux symptoms.

4. **EMOTION.** The retarding effect of emotional states on gastric motility and secretion has been documented by clinical and experimental observations. In healthy humans, anger, fear, labyrinthine stimulation, painful stimuli, preoperative anxiety, and intense exercise slow gastric empty-

ing. The influence of emotions on gastric activity may be augmentative or inhibitory, depending on whether the emotional experience is of an aggressive (hostility, resentment) or depressive (sorrow, fear) type, respectively.

5. **PAIN.** Severe or sustained pain in any part of the body (as from a kidney or gallbladder stone, migraine, or sciatic neuritis) inhibits gastric motility and evacuation by nervous reflex pathways.

HORMONAL FACTORS INFLUENCING GASTRIC ACTIVITY

The stomach has multiple functions, which include digestion, secretion of acid, storage of food, and absorption. It is also involved in the regulation of appetite and satiety. Gut peptides play a major role in each of these diverse functions by modifying secretion, motility, and appetite regulation. More than 100 bioactive peptides have been discovered and function in autocrine, paracrine, or neurocrine ways. Five peptides, gastrin, CCK, secretin, somatostatin, and motilin, directly influence gastric activity and are described here in more detail.

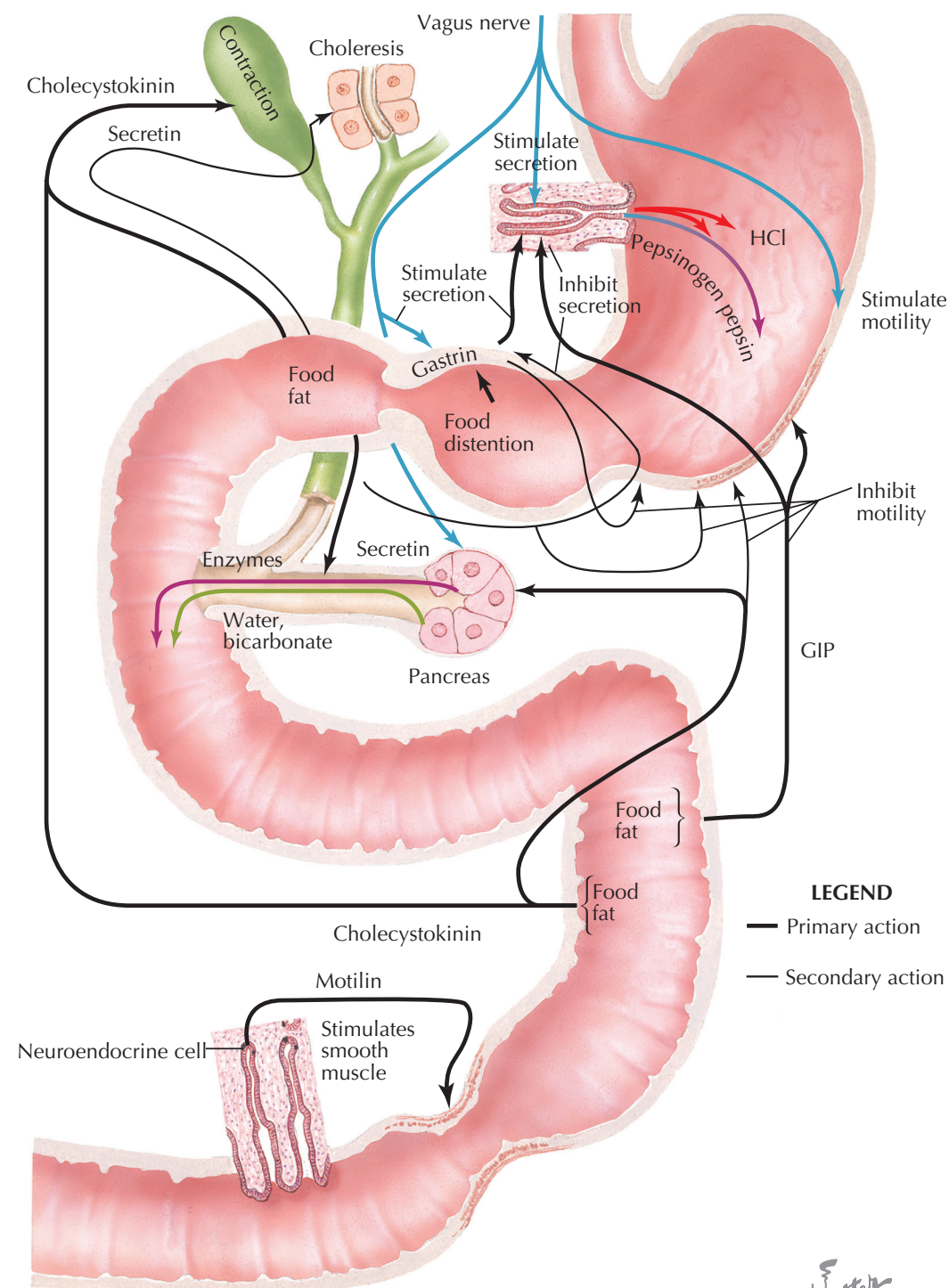
Gastrin is produced mainly in the G cells of the gastric antrum in response to a meal or a high gastric pH. G cells are tightly regulated by gastrin-releasing peptide, somatostatin, and vagal inputs from the parasympathetic nervous system. Gastrin is a major mediator of gastric acid secretion and acts by inducing the secretion of histamine, which, in turn, stimulates hydrochloride secretion. The most common cause of elevated gastrin levels is use of acid-suppressive medications, specifically proton pump inhibitors, which inhibit somatostatin release (a potent inhibitory stimulus) from the antral D cells. Other important causes of hypergastrinemia include the atrophic gastritis often associated with *H. pylori* infection and Zollinger-Ellison syndrome. The latter is a rare disorder caused by a gastrin-producing tumor commonly located in the *gastrinoma triangle*, bounded by the neck of the pancreas, the duodenum, and the cystic and common bile ducts. The serum gastrin in patients with a gastrinoma can be higher than 1000 pmol/L. The syndrome typically presents with peptic ulcers, diarrhea, and abdominal pain.

Cholecystikinin (CCK) is a peptide produced by the I cells of the duodenum and jejunum and belongs to the family of “brain-gut” peptides, in which the same transmitter is found in the intestine and CNS. The primary stimulus for its secretion is the presence of long-chain fatty acids, monoglycerides, or proteins in the small intestine. CCK is a potent stimulator of gallbladder contraction and also relaxes the sphincter of Oddi, which facilitates flow of bile into the intestine. CCK is a potent inhibitor of acid secretion by activating somatostatin release via CCK 1 receptors. Over the past few decades, understanding of CCK’s role in regulation of meal ingestion satiety has increased. Following postprandial secretion, it delays gastric emptying. CCK also acts on vagal afferent nerve fibers and sends signals to the dorsal hindbrain to reduce meal size and increase the intermeal interval.

Secretin is a peptide secreted by the S cells in the duodenum and jejunum in response to a low duodenal pH. Secretin stimulates pancreatic fluid and bicarbonate secretion, leading to neutralization of acidic chyme in the intestine. Secretin also stimulates fluid and bicarbonate release from the biliary ducts, duodenal mucosa, and Brunner glands while inhibiting gastric acid release and intestinal motility.

Somatostatin is abundant in the gastrointestinal tract and pancreas, where it is produced by paracrine D cells. Somatostatin secretion is stimulated by meal ingestion and gastric acid secretion. Somatostatin is a key inhibitory peptide. It decreases endocrine and exocrine secretion, reduces gastrointestinal motility and blood flow, and inhibits gallbladder contraction and secretion of most gastrointestinal hormones.

Motilin is a peptide secreted by the M cells of the proximal small intestine. It is released in the interdiges-



LEGEND

- Primary action
- - - Secondary action

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tive state and triggered by luminal alkalization and bile. On the other hand, the presence of nutrients or acid in the small intestine strongly suppresses the endogenous release of motilin in a digestive state. The motilin receptor activates the phospholipase C signaling pathway expressed in nerves and smooth muscles. Circulating motilin levels peak every 1 to 2 hours in fasting individuals. Motilin is thought to facilitate the phase III migrating motor complex, often known as the intestinal housekeeper, which is a strong contraction that begins

at the lower esophageal sphincter and progresses down the gastrointestinal tract, sweeping nondigestible solid residue toward the colon and preventing colonic bacteria from migrating into the small bowel.

The motilin receptor also binds and is activated by the macrolide antibiotic erythromycin, which is used in the off-label treatment of delayed gastric emptying seen in diabetes mellitus and in patients with duodenectomy. However, its broad range of activities limits long-term use.

FUNCTIONAL CHANGES IN GASTRIC MOTILITY AND SECRETION IN GASTRIC DISEASES

Gastric secretion and motility vary considerably from one individual to another and in the same individual from time to time. In the stomachs of subjects in whom no disease of the upper gastrointestinal tract can be demonstrated, the emptying time of a standard meal may vary over 100% from the average, and the concentration of HCl (acid) secreted in the basal state or in response to the standard stimuli ranges from 0 to 100 mEq/L or more.

DUODENAL ULCER

A tendency to gastric hypertonicity and hypermotility is observed in many duodenal ulcer patients. Initial emptying of a meal may be delayed for a considerable time because of reflex antral spasm incited from the ulcerated duodenal bulb; after the pressure by the active contractions of the stomach overcomes the pyloroantral resistance, evacuation proceeds rapidly, so that the final emptying time may be considerably shortened. The most important motility change occurs when the ulcer area becomes inflamed and edematous, or scarred, so that the gastric outlet is obstructed. After a preliminary period of hypermotility, the stomach becomes atonic, a condition immediately recognized roentgenographically with the first swallow of barium. The stomach, in cases of duodenal ulcer, tends to secrete *excessive acid*, in both volume and concentration, so that the average output of acid in duodenal ulcer patients greatly exceeds the average of all other categories, including the normal. The rare disease described by Ellison and Zollinger is characterized by peptic ulceration in the upper intestine distal to the duodenal bulb and secretion of enormous quantities of gastric acid.

It is not certain whether hypersecretion exists before the duodenal ulcer starts to develop, but it does persist after the ulcer heals. This may be due to an underlying *H. pylori* infection affecting the inhibitory D cells of the stomach secreting somatostatin that normally inhibits gastric acid secretion.

The pain in duodenal ulcer is most often described as a gnawing or intense hunger sensation, coming on characteristically from 1 to 2 hours after a meal.

GASTRIC ULCER

The pathophysiologic phenomena caused by a gastric ulcer depend on the site of the ulcer in the stomach. The closer the ulcer is to the pylorus, the more the manifestations resemble those of duodenal ulcer. In peptic ulcer of the lesser curvature at or proximal to the incisura, gastric motility is not notably altered from normal, except for some local hypertonicity of the musculature at, and frequently opposite, the ulcer site. When the gastric emptying is delayed in a case of ulcer of the body of the stomach, the presence of a coexisting duodenal ulcer should be suspected. The gastric stasis resulting from chronic pyloric narrowing by a duodenal ulcer may be a factor for formation of a gastric ulcer.

The pain of gastric ulcer tends to occur relatively soon after eating, because the gastric acid content is in immediate contact with the lesion. For this reason, smoothness and blandness of the diet are much more important in a gastric than in a duodenal ulcer. Now that proton pump inhibitors are used in treatment, eating a bland diet has become less important.

	Normal	Duodenal ulcer	Gastric ulcer	Gastric cancer	Atrophy
Gastric motility					
Gastric secretion					
Pain (relationship to meals and character)	 No pain 	 Onset 1 to 2 hours after meal Epigastric gnawing pains 	 Onset 1/2 to 1 hour after meal Epigastric gnawing pains 	 Onset shortly after meal Epigastric fullness, distress 	 Variable; immediately to 4 hours after meal Epigastric fullness, distress

GASTRIC CANCER

Gastric carcinoma is not characterized by any general motility pattern, except for the obvious changes to be expected in an area of infiltration into muscle or where the tumor produces obstruction.

GASTRIC ATROPHY

In atrophy of the gastric mucosa (schematically indicated in the picture by a flattened mucosal surface, although the thinning of the mucosa by loss of the normal glandular arrangement does not necessarily result in obliteration of the rugal folds), the reduction in glandular

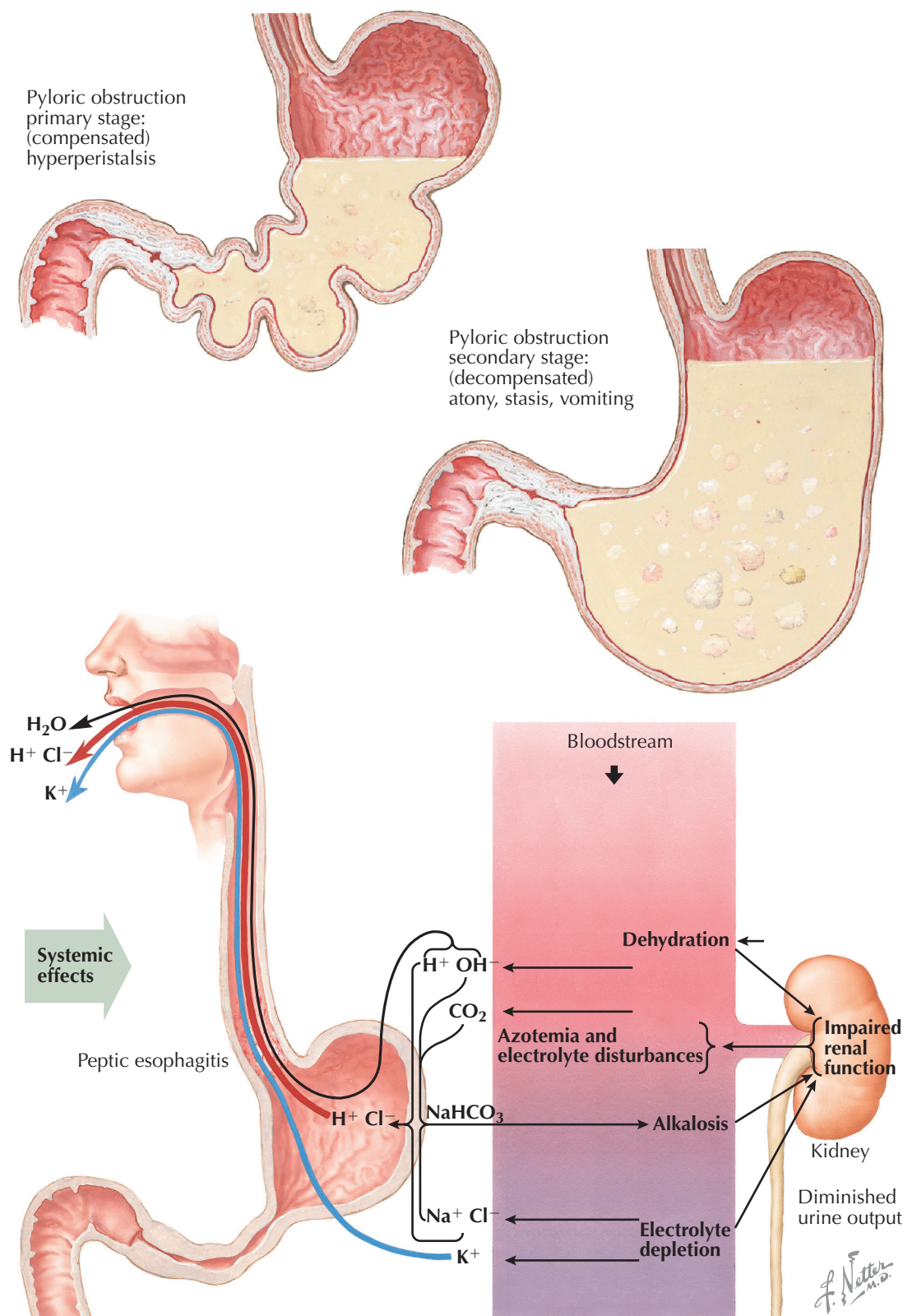
elements results in greatly diminished acid secretion and often no HCl secretion even with maximal stimulation. The reduction of gastric acid results in a secondary elevation of the systemic hormone gastrin, trying to signal to increase gastric acid secretion. Thus, an elevated serum gastrin level may be seen in either Zollinger-Ellison syndrome or pernicious anemia with its gastric atrophy. Differentiation of these two entails the presence of ulcers in Zollinger-Ellison syndrome or measuring gastric acidity (low in pernicious anemia but high in Zollinger-Ellison syndrome). If motility is affected at all in gastric atrophy, it is in the direction of a decrease.

PYLORIC OBSTRUCTION; EFFECTS OF VOMITING

When the outlet of the stomach at the pylorus becomes narrowed to the point of interference with gastric emptying, the *gastric musculature responds at first with increased peristalsis* in an effort to build up sufficient pressure to overcome the resistance at the stomach's pyloric end. At this stage, the patient experiences a sensation of "burning" in the epigastrium or left hypochondrium. With persisting obstruction and further stagnation of the stomach contents, both of ingested food and of gastric secretions, the *stomach begins to dilate*; the musculature becomes atonic, and very little peristaltic activity is present. The patient now complains of fullness, vomiting (in the late afternoon or evening or during the night) of undigested food eaten many hours earlier, and foul eructation. If the obstruction is unrelieved, vomiting becomes more frequent and more copious. With so little gastric contents now passing into the intestine because of the profound gastric atony and pyloric obstruction, the patient is not able to keep up with the *fluid and electrolytes lost* in the vomitus; dehydration, hypochloremia, hypokalemia, and alkalosis supervene. These, in turn, affect renal function, with the consequent development of oliguria, azotemia, and retention of other electrolytes. Clinically, the patient is weak, anorexic, and drowsy. Unless measures are instituted to correct the metabolic disorder and relieve the obstruction, the condition progresses to irreversible tissue damage and a fatal outcome.

Pyloric obstruction is not the only cause of vomiting. *Gastroparesis* is a more common cause, with delayed gastric emptying often from antral hypomotility without any pyloric obstruction. The diagnosis of pyloric obstruction may be suspected by the preceding history, the pattern of the emesis, the appearance of the vomitus, and the presence on physical examination of a *succussion splash* (splashing of gastric contents heard on auscultation when gently rocking the patient). In *duodenal ulcer*, which is the most common cause of pyloric obstruction, the patient usually gives a history of ulcer symptoms. The vomiting is at first intermittent, perhaps at intervals of 2 or 3 days, and the vomitus often contains recognizable particles of food eaten the previous day. The quantity of fluid and ions lost by vomiting is largely dependent upon the degree of gastric dilatation and, thereby, upon the length of time during which the pyloric obstruction develops and remains incomplete (i.e., upon the time between the *primary stage*, in which the obstruction is "compensated for" by increased peristalsis, and the *secondary stage*, in which the stomach becomes atonic).

As with any excessive vomiting from whatever cause, the *patient loses* appreciable amounts of *fluids, hydrogen ions, chloride ions, and potassium*. The loss of potassium is attributable to the fact that the parietal cell secretes significant amounts of this ion. Because the gastric juice is poor in sodium, usually no sodium deficiency occurs,



and while sodium remains in the blood, the bicarbonate ion substitutes for the chloride ion.

Vomiting does not ordinarily occur in uncomplicated ulcer disease, except when the ulcer is located in the pyloric canal, but many ulcer patients empty the stomach by means of vomiting to obtain relief from the pain.

Management of the consequences of repeated or excessive vomiting consists of fluid and electrolyte replacement and evacuation of the stomach with a

nasogastric tube for 24 to 72 hours. If the obstruction itself is not relieved, surgery is necessary to reestablish gastrointestinal passage, but it should not be undertaken before the fluid and electrolyte balance has been restored.

A clinical and physiologic disturbance closely resembling that of pyloric obstruction may result from excessive ingestion of a soluble alkali and a rich source of calcium, such as milk; this is called the *milk-alkali* or *Burnett syndrome*.

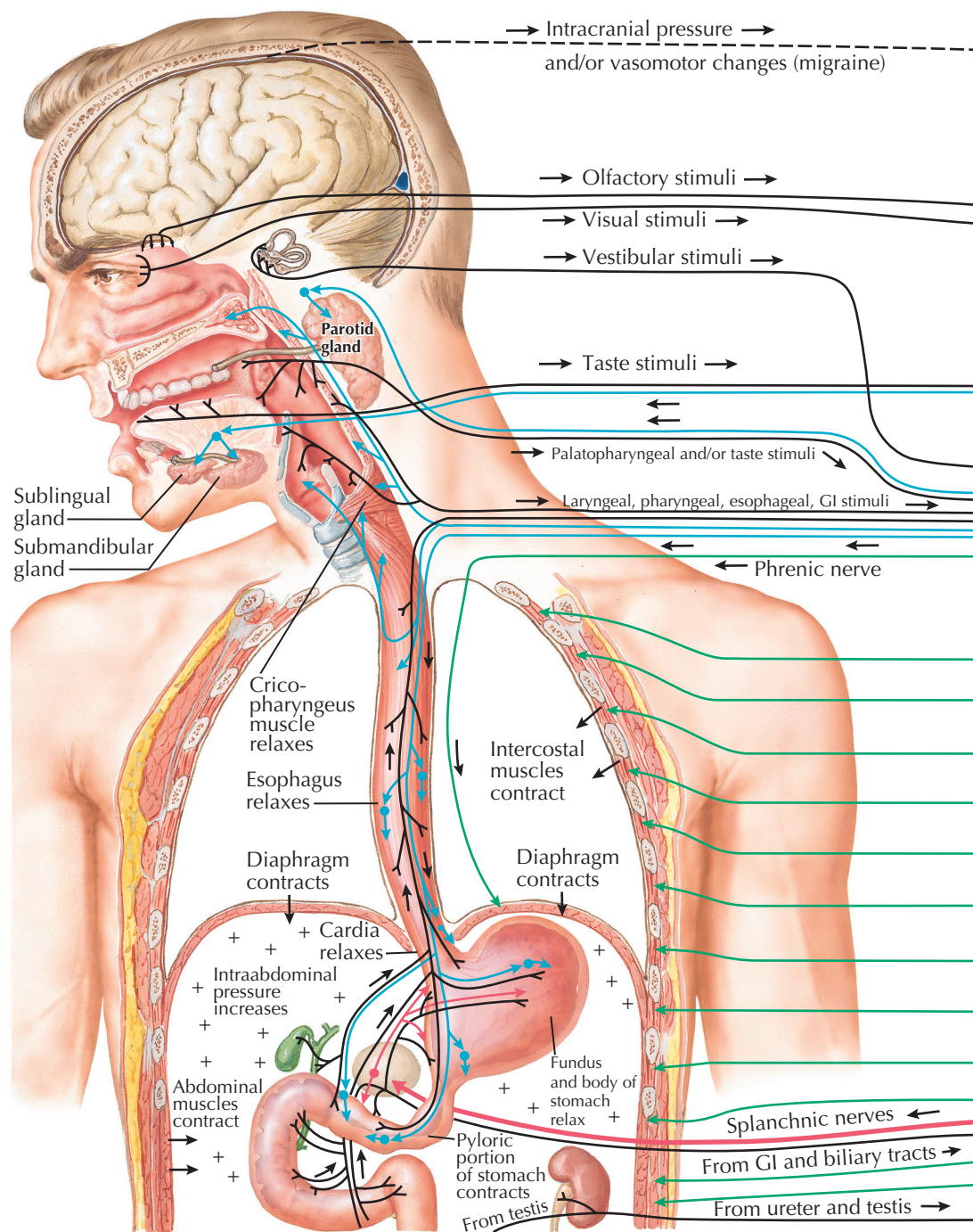
NAUSEA AND VOMITING

Having the symptom of nausea is a disagreeable experience that is difficult to define as well as distressing to experience. Nausea is often described as a sick feeling or a feeling of imminent vomiting. Nausea generally precedes vomiting; a notable exception to this is vomiting because brain tumors are present. Nausea may occur, continuously or in waves, without vomiting, especially if the stomach is empty. Salivation, pallor, tachycardia, faintness, weakness, and dizziness are frequent concomitants.

The biologic purpose of nausea may be the prevention of food intake, and of vomiting the expulsion of food or other substances already ingested, in circumstances where their presence in the upper gastrointestinal tract is unfavorable to the functioning of the organism. For instance, the loss of gastric tonus and peristalsis, which occurs in motion sickness, may make it expedient for the gastric contents to be gotten rid of in that condition. Because nausea and vomiting may result from disturbances in practically any part of the body, the teleologic significance of these symptoms is not always apparent; indeed, in certain situations they appear to be contrary to the welfare of the individual.

Nausea and vomiting may be precipitated by emotional disturbances; by intracranial vasomotor and pressure changes; by unpleasant olfactory, visceral, or gustatory stimuli; by functional or anatomic alterations in the thoracic and abdominal viscera, including the urogenital tract; by intense pain in somatic parts; by exogenous or endogenous toxins; by drugs (notably the opiate narcotic analgesics); and by stimulation of the vestibular apparatus (most commonly by motion). Impulses from all of these sources reach the CNS via the corresponding sensory nerves. It is possible that the medullary emetic elements make ascending connections with some cortical area concerned in the perception of nausea, and that these connections are activated before the impulses stimulating the emetic mechanism have reached the vomiting threshold.

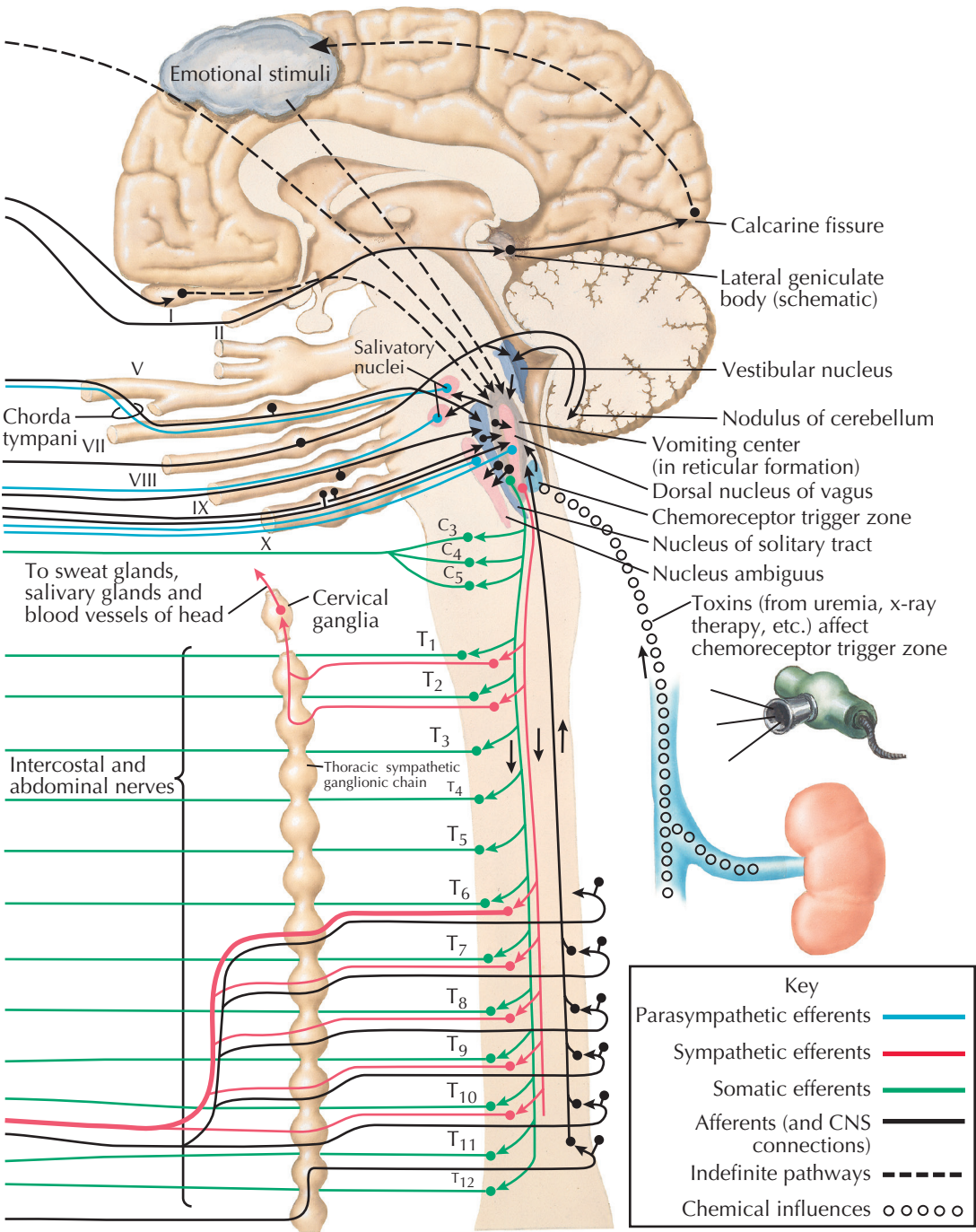
The CNS control of vomiting is vested in two areas: one, called the *vomiting center*, is located in the *lateral reticular formation* of the medulla, in the midst of the cell groups governing such related activities as salivation and respiration. The other, called the *chemoreceptor*



trigger zone, is in a narrow strip along the floor of the fourth ventricle in close proximity to the vomiting center. The functions of the two areas are distinct, though not independent. The vomiting center is activated by impulses from the gastrointestinal tract and other peripheral structures. The chemoreceptor trigger zone is stimulated by circulating toxic agents and by impulses from the cerebellum; influences of this zone on the vomiting center produce the resulting emetic action. Thus, ablation of the chemoreceptor zone abolishes the emetic response to apomorphine, a centrally acting emetic, and to intravenously injected copper sulfate, which acts in the same way, but not to orally administered copper sulfate, because the latter exerts a peripheral action via the autonomic nerves to the vomiting center. Ablation of the vomiting center, on the other hand, abolishes the emetic response to apomor-

phine and to injected copper sulfate, because vomiting does not occur when the vomiting center is destroyed.

Vomiting may be analyzed as follows: Impulses set up by irritation in any somatic or visceral parts or in any of the sense organs pass, by way of their respective sensory nerves, to reach the medulla, where they activate the vomiting center; toxic agents, whether introduced into the body or accumulated endogenously, act upon the chemosensitive trigger zone, from whence impulses reach and activate the nearby vomiting center. Before the vomiting threshold is exceeded, impulses passing up to the cortex give rise to the sensation of nausea. The vomiting center coordinates the discharge of impulses from adjacent neural components to the various structures that participate in the act of vomiting. *Salivation*, which almost invariably precedes the actual ejection of the vomitus, is stimulated by impulses



component, as is evident from the fact that some individuals develop the symptoms merely from being rotated or from riding backward in a train. In such instances, attempts to resolve the visual disorientation by movements of the eyes and head may result in stimulation of the labyrinth, either directly or by the fall in gastric tonus which may occur with eye movements of this type. That visual stimuli are not essential for the development of motion sickness is evident from the fact that even blind persons may be susceptible.

Rapid downward motion that comes to a sudden stop or is followed by upward motion causes the abdominal viscera to sag and pull on their attachments; this is the origin of the sinking feeling experienced at the end of a rapid descent in an elevator or in a sudden sharp drop in a plane. The sensation would not occur if a person were to do a headstand in an elevator, and it would be reduced if a person were in a horizontal position when a plane was bouncing up and down, because the viscera cannot be displaced as far in the anteroposterior as in the craniocaudal direction. Nausea and retching may be induced in a patient under spinal anesthesia by downward traction on the exposed stomach. Impulses set up by these visceral stimuli pass in the autonomic nerves, chiefly the vagus nerves, to the vomiting center. Yet the vestibular mechanism is in some way concerned in the effect, because motion sickness does not occur in the absence of the vestibular organs.

Impulses mediating nausea and vomiting by vestibular stimulation originate principally in the utricular maculae of the labyrinth, pass by way of cranial nerve VIII to the vestibular nuclei, to the uvula and *nodulus of the cerebellum*, to the chemoreceptor trigger zone, and, finally, to the vomiting center.

Nausea, besides being an unpleasant symptom that is sometimes difficult to relieve, becomes a serious clinical problem if it is sufficiently prolonged to interfere with nutrition. Primary nausea (i.e., nausea occurring in the postabsorptive state) occasionally accompanies eye strain, myocardial infarction, azotemia, and visceral neoplastic disease.

Protracted vomiting is detrimental not only from the nutritional standpoint but also because of electrolyte depletion and the possible development of tears of the gastroesophageal mucosa which may bleed (*Mallory-Weiss syndrome*) and of esophagitis. If vomiting does not respond to the administration of antiemetic drugs, nasogastric suction can be instituted; correction of a gastric hypotonus may prove to be the factor that brings the condition under control.

NAUSEA AND VOMITING
(Continued)

from the salivary nuclei. Contraction of the *intercostal muscles* and of the *diaphragm* produces a sharp inspiratory movement and *increased intraabdominal pressure*, an effect that is abetted by *contraction of the abdominal muscles*. Closure of the glottis forestalls aspiration into

the respiratory passages. The *pyloric portion of the stomach contracts*; the body of the stomach, the *cardia*, the *esophagus*, and the *cricopharyngeus muscle relax*; and the gastric contents are forced out through the mouth and, in a vigorous emesis, through the nose as well.

Nausea and vomiting, brought on by motion, result from stimulation of the *vestibular organs* by movements of the head, neck, and eye muscles, and by traction on the abdominal organs. The type of motion necessary to precipitate motion sickness does not require a vertical

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AEROPHAGIA AND BELCHING

Aerophagia is described as objectively observed or measured air swallowing. Aerophagia usually leads to troublesome repetitive belching. These symptoms must occur at least 3 times a week for over 6 months to be considered a functional gastrointestinal disorder by the ROME criteria, a consensus gastrointestinal guideline. Aerophagia with belching is seen more commonly in developmentally disabled or anxious persons but can be seen in any population.

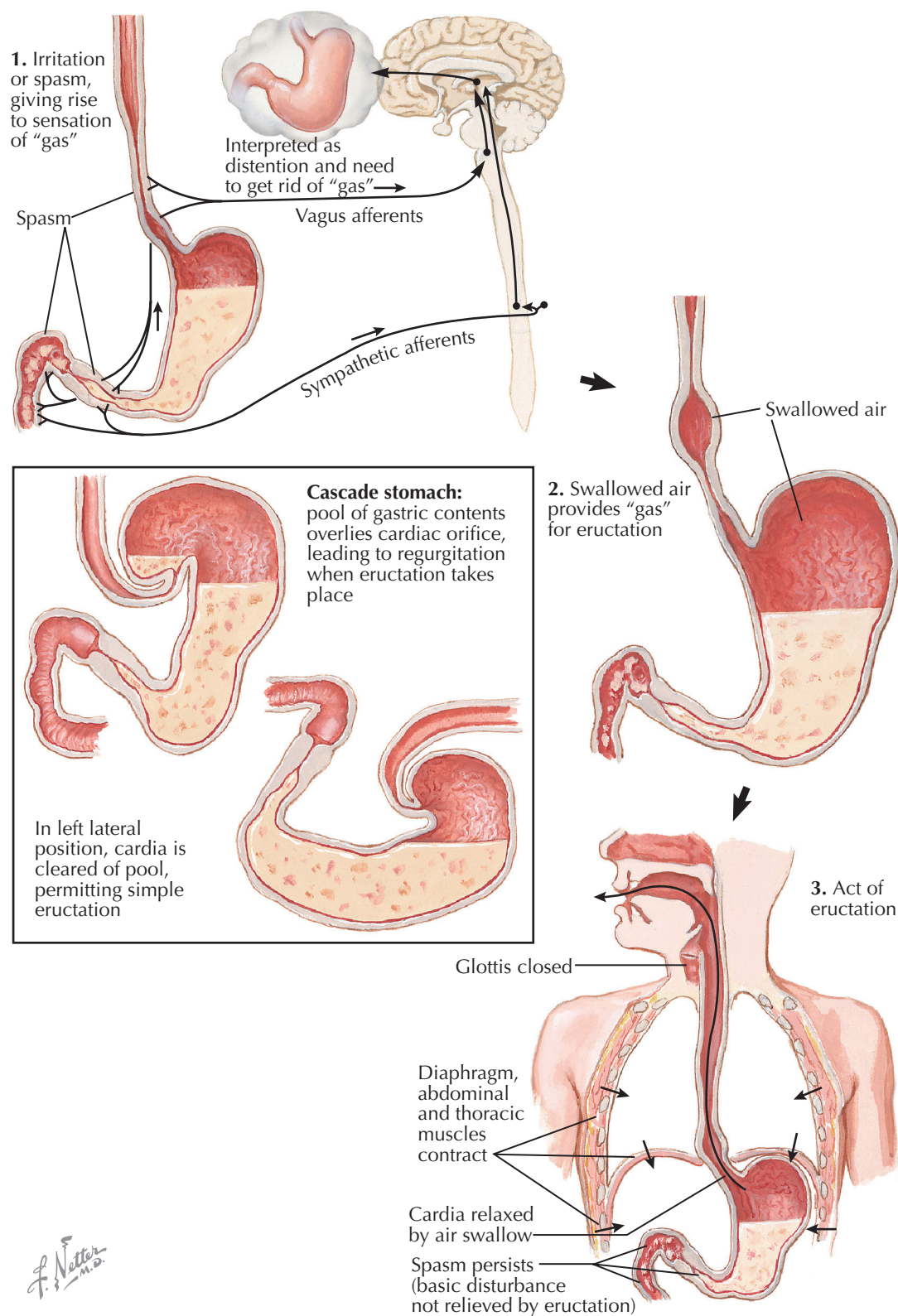
There are various pathophysiologic mechanisms by which aerophagia occurs. For one, a person can swallow air and retain it in the esophagus. This can occur voluntarily or in conditions in which the lower esophageal sphincter remains tight, such as achalasia. Aerophagia occurs during normal daily activities such as swallowing saliva; however, it can be exacerbated by certain lifestyle factors such as rapid ingestion of food, smoking, chewing gum, or drinking carbonated beverages. Physical activity with deep breathing, mouth breathing, and the use of a continuous positive airway pressure device can also lead to increased aerophagia. Hyperventilation when nervous or mouth breathing due to nasal or sinus disorders also is a common cause.

The consequence of aerophagia is usually belching, also known as burping or eructation. In the act of belching, the glottis is closed and the diaphragmatic and thoracic muscles contract when the increased intraabdominal pressure transmitted to the stomach is sufficient to overcome the resistance of the cardia and the physiologic lower esophageal sphincter; the swallowed air is expelled via a burp. Belching can become a chronic disorder with habit-forming potential.

Belching occurs from the beginning of life and is frequently seen in infants, who often swallow air while drinking milk. In adults, belching may occur because of overdistention of the stomach after a large meal. Certain foods such as broccoli, beans, cauliflower, and other high-fiber foods can predispose to gas formation and, in turn, belching. Food substitutes and medications that are poorly digested may lead to gas and burping. Examples include sorbitol, which is used frequently as a sugar substitute, and lactulose, which is used in patients with constipation or hepatic encephalopathy. Inflammation of the stomach from disorders such as gastritis or peptic ulcer disease can also lead to stomach discomfort and the need to belch. Lastly, transient lower esophageal sphincter relaxations that occur spontaneously while a person is upright and awake can lead to the release of air from the stomach.

The diagnosis of aerophagia is often made by careful history taking. Repetitive belching can also be diagnosed by the history, although sophisticated tools such as esophageal manometry, esophageal impedance, or impedance pH testing may indicate that it is occurring. An increase in abdominal pressure coupled with retrograde reflux and subsequent relaxation of the upper esophageal sphincter signifies belching; other conditions, such as rumination, can also have these signs, however.

Rarely does aerophagia or belching lead to worrisome complications. The potential for gastric volvulus, intestinal ileus, or perforation can theoretically exist with excessive aerophagia, but they are rare and mainly seen in developmentally disabled persons. These patients can be challenging because they may not be able to follow recommendations. In these cases, other



measures to decompress the stomach or colon may be needed. Nasogastric, gastrostomy, or rectal decompression tubes may be necessary to avert complications. More commonly, aerophagia and belching are not at all dangerous, and the main consequences are bothersome symptoms for the patient or his or her family. Although patients often seek out medical advice for these troublesome symptoms, they are often relieved to hear that neither condition is life threatening. The best therapy for aerophagia and belching is education and behavioral

modifications. Investigations for pathologic conditions such as gastroesophageal reflux disease (GERD) or peptic ulcer disease may be completed but are generally unhelpful. For individuals who suffer from discomfort from aerophagia, positional maneuvers can be helpful. Lying on the left lateral side or bringing the knees up to the chest may help slowly release air without overt belching. Although their effectiveness has not been proven, other treatment regimens include breathing exercises, biofeedback therapy, and hypnosis.

ENDOSCOPIC EVALUATION OF THE STOMACH: UPPER ENDOSCOPY

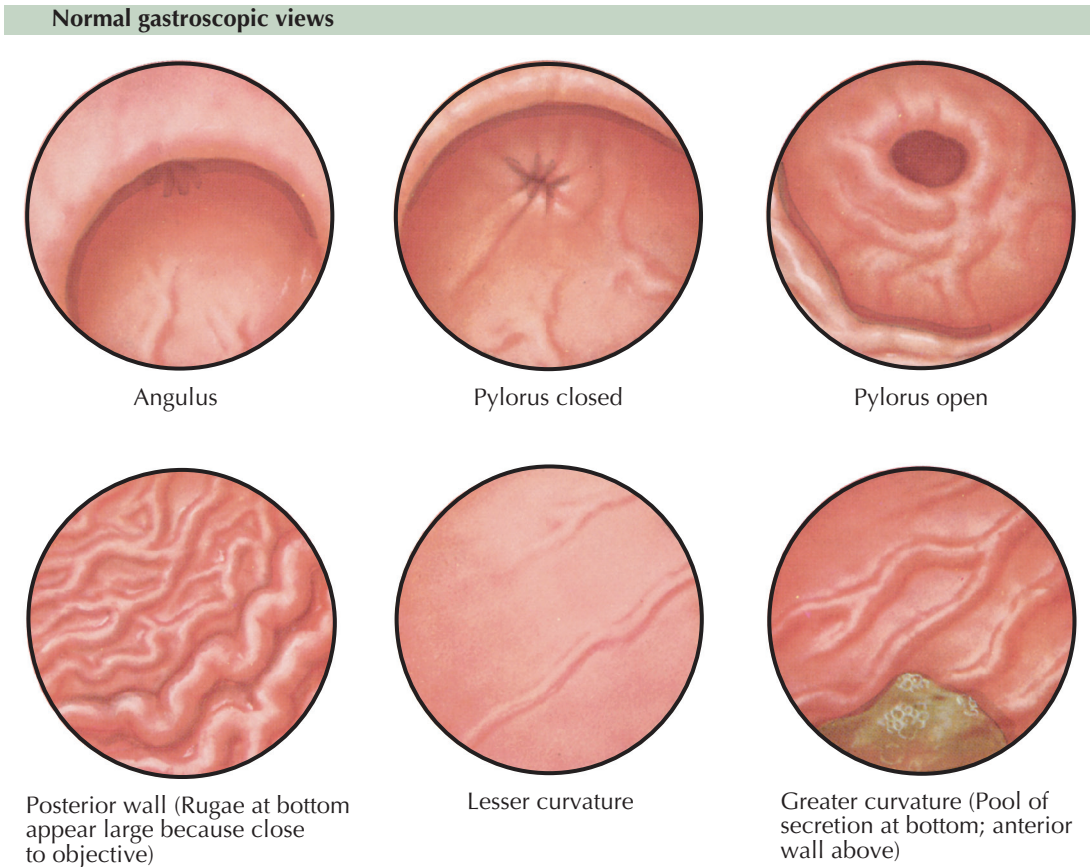
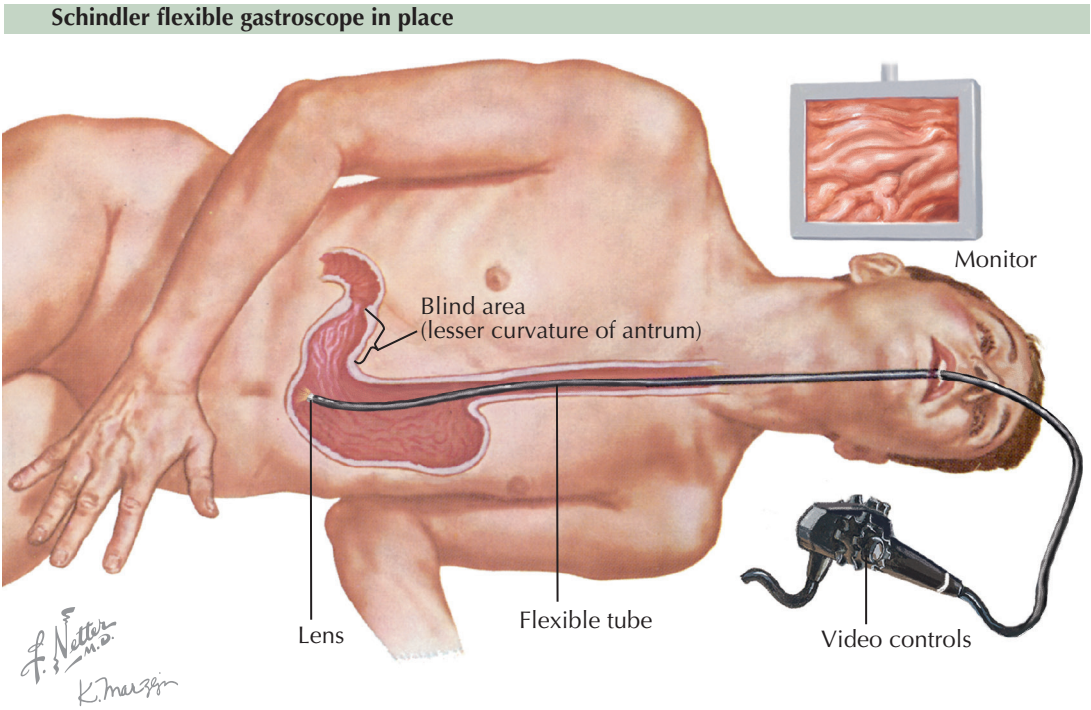
Gastroscopy, esophagogastroduodenoscopy, or upper endoscopy is a procedure performed by a gastroenterologist that allows for visualization of the esophagus, stomach, and duodenum. It is an essential procedure used for both the diagnosis and treatment of disorders of the upper gastrointestinal tract. The examination has evolved from using rigid and semirigid instruments with fiberoptics to currently flexible instruments and videoendoscopy. At the tip of the endoscope there is a color chip that gathers images that are electronically transmitted to a video processor and a monitor in the endoscopy examination room. A light at the tip of the endoscope allows for illumination. Images are taken during the examination and can be stored. Endoscopes, which are typically 8 to 10 mm wide, also have a channel for biopsy. At the control head there are buttons that allow for air insufflation and suctioning of fluid and air.

There are a number of indications for upper endoscopy, including dysphagia, GERD, eosinophilic esophagitis, Barrett esophagus, gastric metaplasia, peptic ulcer disease, dyspepsia, *H. pylori* infection, celiac disease, and management of upper gastrointestinal malignant lesions. Upper endoscopy has several therapeutic uses, including hemostasis of bleeding ulcers, varices, Dieulafoy lesions, and arteriovenous malformations; removal of foreign objects; dilation of the esophagus; and stent placement.

Prior to performing upper endoscopy, it is key to understand the indication for the procedure as well as the risks and benefits for each case. Upper endoscopy can be performed on an elective, urgent, or emergent basis. Some of the most common indications for upper endoscopy are listed above. Complications to be cognizant of include excessive bleeding, infection, perforation, aspiration, cardiopulmonary events, and adverse reactions to anesthetic agents.

For upper endoscopy, a moderate level of sedation is used to reduce pain and induce sedation. The medications used vary, but typically a combination of a short-acting benzodiazepine and opiate or propofol is used. In addition, local anesthetics can be gargled, sprayed, or applied directly to the pharynx to suppress the gag reflex during upper endoscopy.

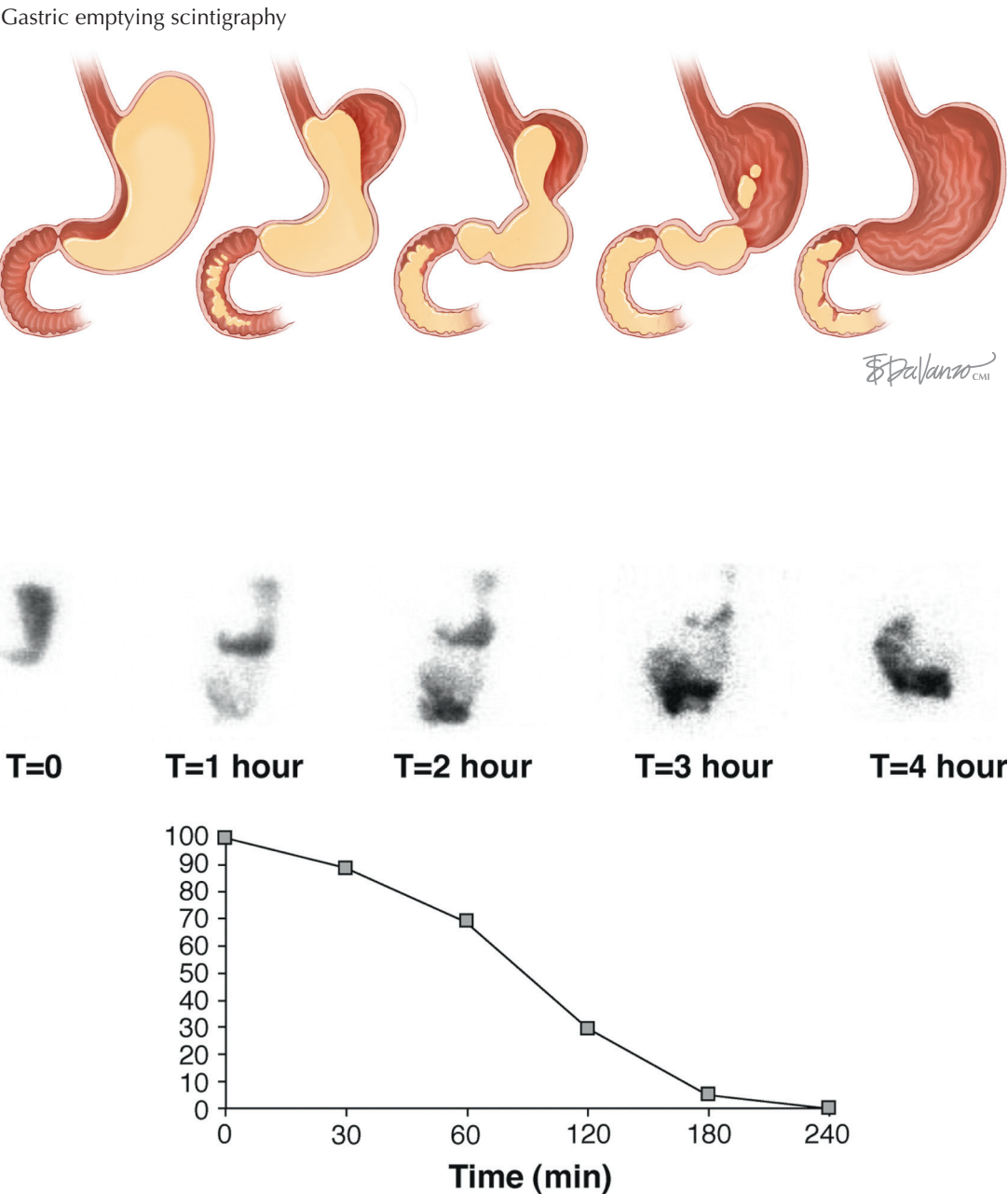
Once the patient is adequately sedated, the endoscope is passed over the tongue and through the pharynx, typically under direct visualization of the vocal cords. The endoscope passes the pharynx, and the



esophagus is examined and visualized using air insufflation. The gastroesophageal junction is inspected for any mucosal abnormalities. The endoscope enters the stomach, where food or bilious contents may be seen. The endoscope is retroflexed, by turning the tip of the endoscope in a J shape, to permit full visualization of the gastroesophageal junction and the fundus. Hiatal hernias are identified on retroflexion. On examination of the pylorus, contractions can be seen. With mild pressure the endoscope passes through the pyloric

channel into the bulb of the duodenum. The endoscope is advanced to the second portion of the duodenum and, if needed, into the third portion. The ampulla of Vater can be seen on upper endoscopy but is best visualized with a side-viewing instrument.

If any masses or mucosal abnormalities are seen in the esophagus, stomach, or duodenum, biopsies can be taken using a forceps that is placed through the biopsy channel. Specimens are placed in a fixative medium and sent for histologic examination.



DIAGNOSTIC AIDS IN GASTRIC DISORDERS: GASTRIC EMPTYING SCINTIGRAPHY

Gastric emptying can be assessed by several methods: scintigraphy, breath testing, and motility capsule testing. Gastric emptying scintigraphy has been the classic test for measuring gastric emptying of a radiolabeled meal. It is quantitative and physiologic. It is used to assess for gastric emptying disorders (either slow or rapid) in a symptomatic patient (in whom structural or mucosal disorders are often ruled out with upper endoscopic or upper gastrointestinal radiologic studies). It is primarily used to diagnose gastroparesis in a patient who has symptoms of this disorder, such as nausea, early satiety, and postprandial fullness. The test can also assess for rapid gastric emptying, which is seen in the dumping syndrome.

The ^{99m}technetium sulfur colloid–radiolabeled meal consists of a standardized meal (the equivalent of two large eggs plus two slices of bread with jam and water). The radiolabel needs to be cooked into the egg white, so that the radioisotope binds to the solid phase of the test meal. Imaging is performed after meal ingestion with a gamma counter with the patient in the anterior and posterior projections at four time points (0, 1, 2, and 4 hours). Performing scintigraphy over 4 hours helps to detect delayed gastric emptying.

The simplest approach for interpreting gastric emptying studies is to report the percentage of retention at defined times after meal ingestion (usually at 2 and 4 hours). Curve-fitting techniques can calculate the half-emptying time, the time for half of the stomach contents to have emptied from the stomach. Other

(From Parkman HP, Jones MP. Tests of gastric neuromuscular function. *Gastroenterology*. 2009 36(5):1526-43.)

Gastric emptying of a meal from the stomach. The top panel is a schematic. The middle panel shows an example of gastric emptying scintigraphy—the gastric emptying of a radiolabeled meal from the stomach over time. The bottom graph depicts the amount retained in the stomach over time.

parameters of potential use are the lag phase for solids, which represents the time required for trituration of solid food into 1- to 2-mm particles that can then empty through the pylorus. Measurement of gastric emptying of solids is more sensitive than measurement of gastric emptying of liquids for detection of symptomatic gastroparesis (slow gastric emptying) because emptying of liquids is often preserved until the gastroparesis is advanced. In patients who have undergone gastric surgery, a dual solid and liquid emptying test may be helpful because symptoms may result from slow solid emptying or rapid liquid emptying.

Hyperglycemia, smoking, and medications are factors that affect gastric emptying. Marked hyperglycemia with serum glucose levels of 250 mg/dL or more significantly delays gastric emptying in diabetic patients when compared with euglycemia. Blood glucose should be under reasonable control on the day of an emptying test to obtain a reliable measurement of gastric emptying. Smoking during the test can delay gastric emptying. Medications, primarily opiate narcotic analgesics and anticholinergic medications, can delay gastric emptying. It is best to stop these medications for 2 days prior to and during the test to get a reliable assessment of gastric emptying.

DIAGNOSTIC AIDS IN GASTRIC DISORDERS: ANTRODUODENAL MANOMETRY

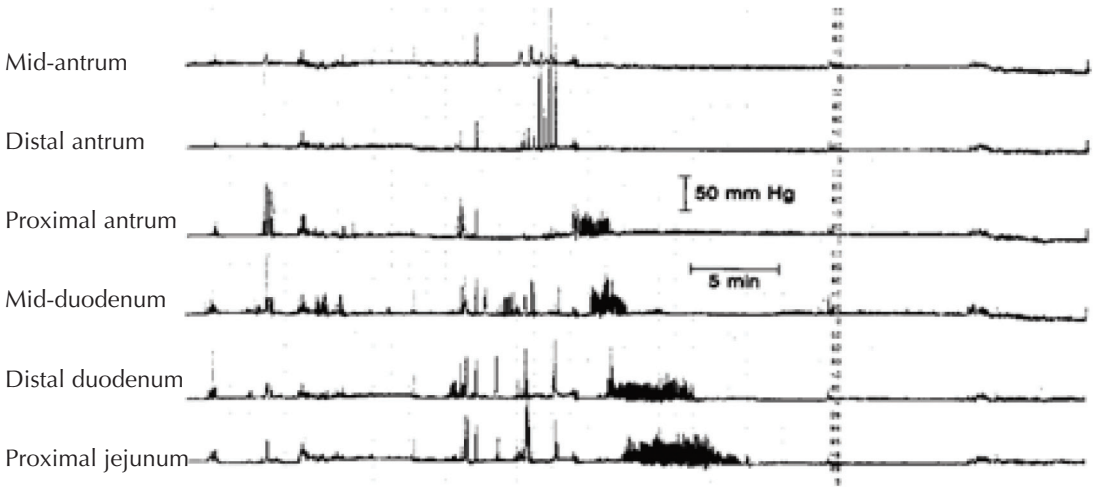
Antroduodenal manometry measures the pressures over time in the antrum and duodenum. The procedure uses a catheter placed either nasally or orally into the stomach and out the pylorus and into the small intestine. The catheter is placed either fluoroscopically or endoscopically. Recordings are obtained from 5 hours (stationary recording) to 24 hours (ambulatory recording), measuring pressures from the stomach and small intestine and the coordination of their contractions, both in the fasting condition and in response to meals. The three main indications for antroduodenal manometry are to evaluate (1) unexplained nausea and vomiting; (2) the cause of gastric or small bowel stasis (e.g., neuropathic or myopathic disorders); and (3) suspected chronic intestinal pseudoobstruction when the diagnosis is unclear.

Decreased antral contractility and the phase III migrating motor complexes originating in the small intestine rather than in the stomach can be seen in gastroparesis. Occasionally, pylorospasm or irregular bursts of small intestinal contractions, which increase outflow resistance, can be observed. With an accurate stationary recording, a reduced postprandial distal antral motility index is correlated with impaired gastric emptying of solids. An average of less than one antral contraction per minute postprandially has been suggested as a simple estimate of significant hypomotility. Ambulatory studies, performed over 24 hours using solid-state transducers, allow correlation of symptoms with abnormal motility, but catheter migration in the stomach prevents quantitation of antral contractility.

Antroduodenal manometry may differentiate between neuropathic and myopathic motility disorders, and it may suggest unexpected small bowel obstruction or rumination syndrome. Myopathic disorders, such as scleroderma or amyloidosis, have low-amplitude contractions (on average, < 10 mm Hg in the small intestine and < 40 mm Hg in the antrum) with normal propagation. Neuropathic disorders have normal



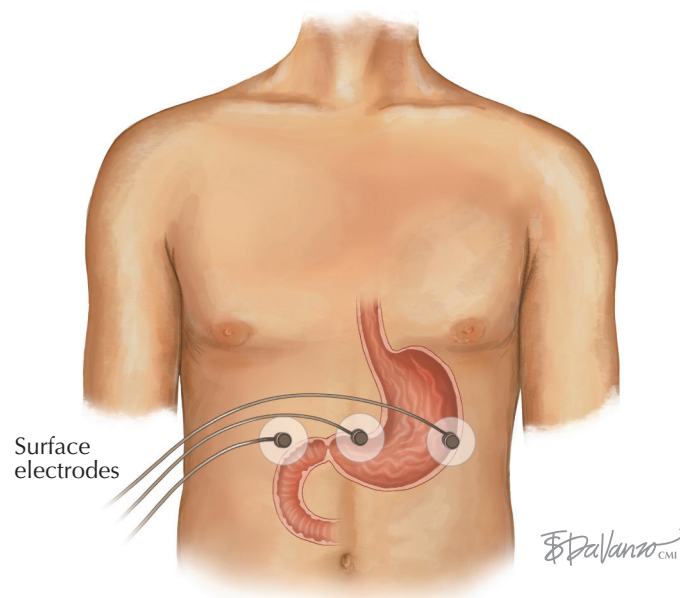
Antroduodenal manometry: fasting state



amplitude but abnormal propagative contractions, seen readily in phase III of the migrating motor complex, such as bursts and sustained uncoordinated pressure activity, and a failure of a meal to induce the fed-type pattern. Occult mechanical obstruction of the small intestine is suggested by two patterns, (1) postprandial clustered contractions for more than 30 minutes separated by quiescence and (2) simultaneous prolonged (> 8 seconds) or summated contractions, suggesting a common cavity phenomenon from a dilated segment

of intestine. Antroduodenal manometry may show a characteristic pattern of rumination; an increase in intraabdominal pressure at all levels of the upper gut (R waves), especially postprandially, indicates the act of rumination.

The absence of migrating motor complexes indicates a poor response to prokinetic agents. Some studies are performed with infusions of erythromycin or octreotide to predict the patient's response to treatment with these agents.



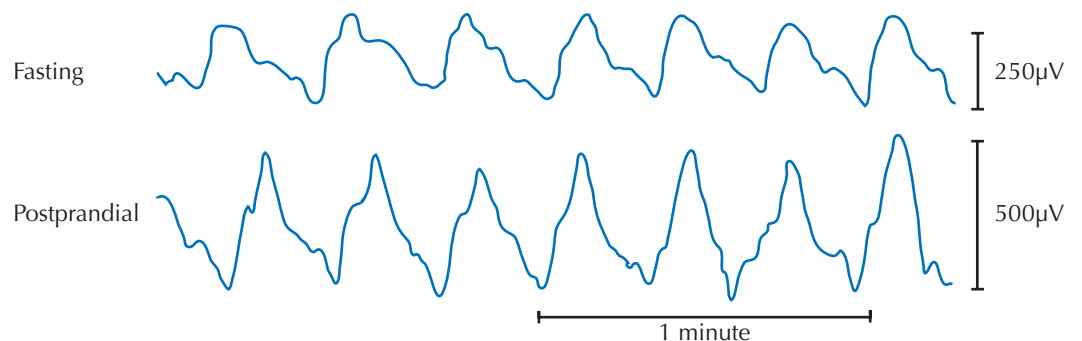
DIAGNOSTIC AIDS IN GASTRIC DISORDERS: ELECTROGASTROGRAPHY

Electrogastrography (EGG) is the recording of gastric myoelectric activity. The technique usually uses superficial abdominal wall electrodes placed on the abdominal skin overlying the stomach. The recorded signal is called an electrogastrogram and usually consists of signals of 3 cycles per minute, reflecting gastric slow wave (pacemaker) activity, which set the frequency for subsequent gastric contractions. Meal ingestion increases the amplitude of the EGG signal by increasing gastric electrical activity and contractility or by distention of the stomach. EGG measures the frequency and regularity of gastric myoelectric activity, detects abnormal rhythms of gastric myoelectric activity, and assesses the amplitude or power increase after a meal.

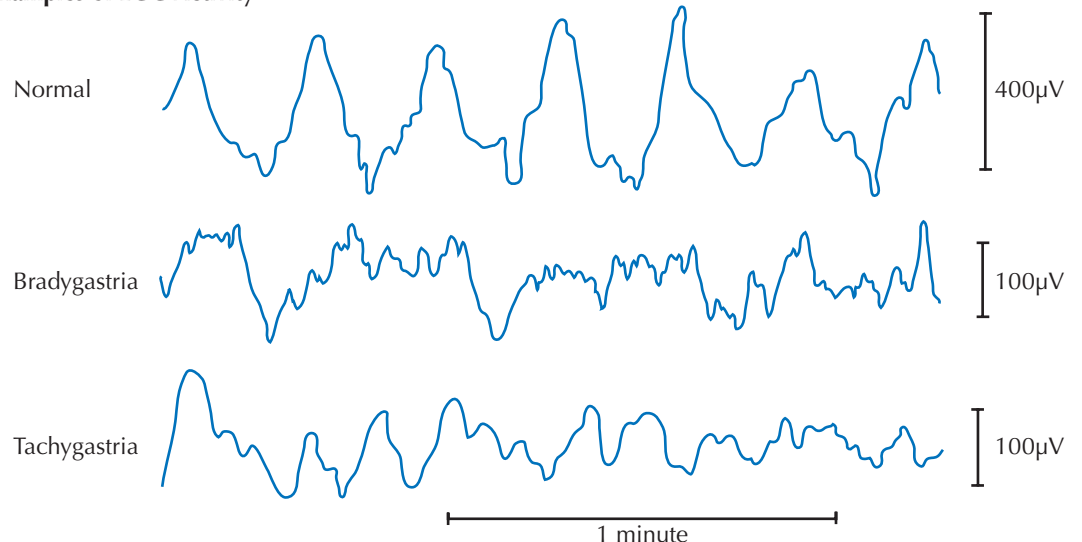
Abnormalities in the EGG signal have been demonstrated in patients with gastroparesis and functional dyspepsia. A significant percentage of these patients may have slow wave frequencies that are very rapid (*tachygastria*) or very slow (*bradygastria*). The gastric electrical slow wave propagation velocity, electromechanical uncoupling, or ectopic gastric pacemaker activity can be detected using more advanced EGG recordings, such as a multichannel recording using electrodes placed at different positions overlying the stomach. EGG can also be recorded with serosal electrodes during surgery.

Gastric dysrhythmias (tachygastria, bradygastria) and decreased postprandial amplitude (or power) of the EGG recording have been described in idiopathic and diabetic gastroparesis. Studies have suggested a good correlation between delayed gastric emptying and an abnormal recording, particularly postprandial rhythm

Normal EGG Activity



Examples of EGG Activity



and amplitude abnormalities. An abnormal recording is made in about 75% of patients with gastroparesis, compared with only 25% of symptomatic patients with normal gastric emptying. Gastric dysrhythmias have been suggested to be better predictors of symptoms than delayed gastric emptying. In diabetic patients, hyperglycemia may provoke dysrhythmias, primarily tachygastrias.

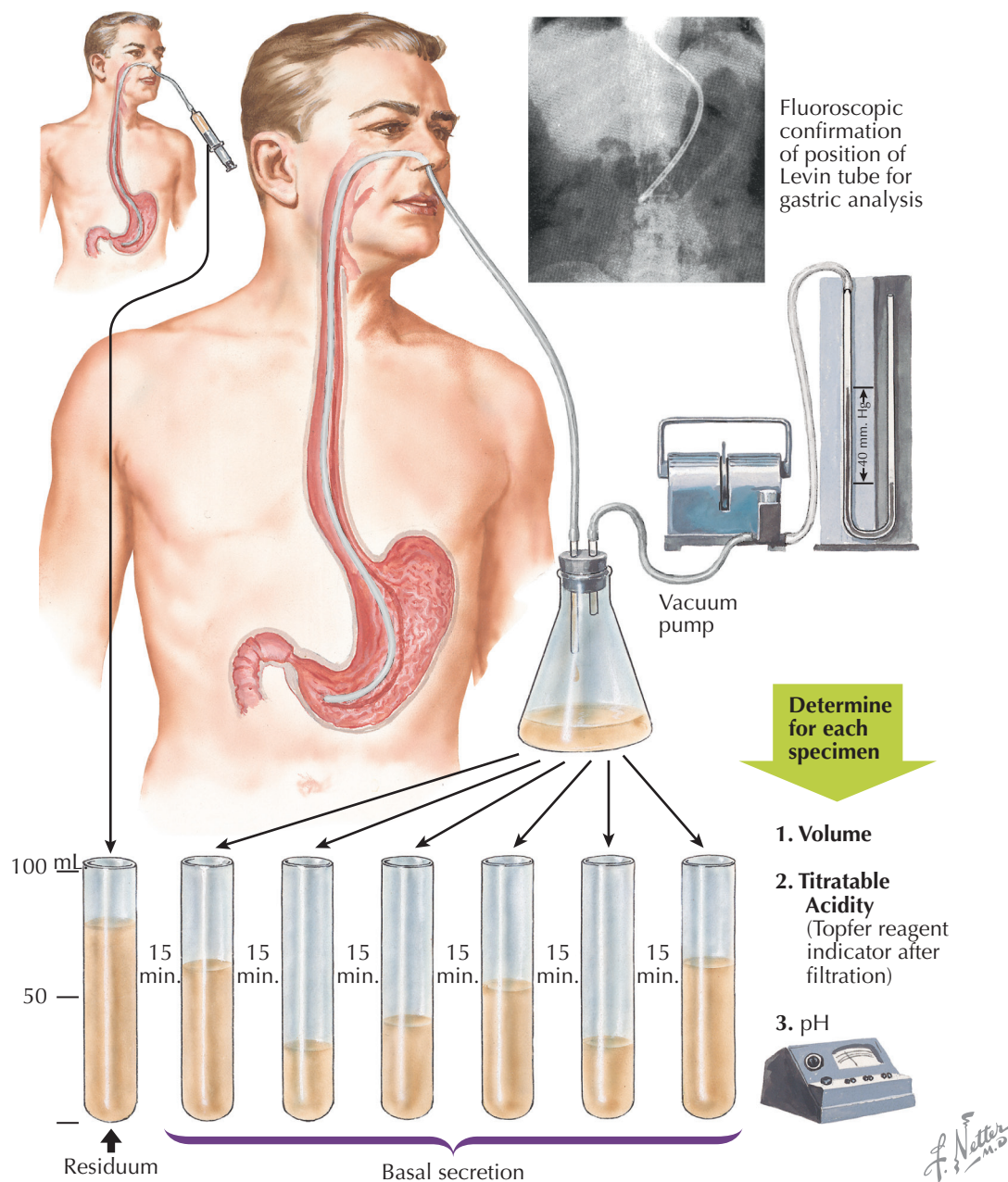
EGG is used to demonstrate gastric myoelectric abnormalities in patients with unexplained nausea and vomiting with abdominal discomfort or functional dyspepsia. The technique is generally used as an adjunct to gastric emptying scintigraphy, as part of a comprehensive evaluation of patients with refractory symptoms suggestive of an upper gastrointestinal motility disorder.

GASTRIC ANALYSIS

Gastric analysis is a technique for measuring acid production of the stomach. Gastric analysis may, in this context, be classified as qualitative or quantitative. A qualitative gastric analysis is undertaken to ascertain whether the gastric glands can secrete acid. A quantitative gastric analysis seeks to determine the amount of HCl secreted by the stomach and is carried out by determining the basal secretion level or the secretory response to insulin hypoglycemia.

Historically, the measurement of acid production provided a useful clinical tool in peptic ulcer disease, pernicious anemia, and management of postvagotomy patients. Because of the discovery of *H. pylori*, the improvements in endoscopy, and the development of proton pump inhibitors, the use of gastric analysis has diminished; it remains a useful diagnostic tool in patients with hypergastrinemia and gastrinoma (Zollinger-Ellison syndrome).

Gastric analysis measures the gastric production of acid over a period of time to determine the *basal acid output* of the stomach. The patient fasts overnight and on the day of the examination, because food in the stomach stimulates acid release and interferes with the determination of basal acid production. A radiopaque nasogastric tube is placed in the most dependent portion of the stomach. If it is positioned correctly, only 5% to 10% of the stomach acid will enter the duodenum and not be collected. The position can be verified with fluoroscopy or through water retrieval. For water retrieval, 20 to 50 mL of water is instilled into the tube and aspirated. Retrieval of at least 90% of the instilled water indicates successful positioning of the tube. Once positioning is verified, continuous gastric aspiration is maintained with negative pressure at 40 to 50 mm Hg. The gastric contents are collected into separate containers at intervals of 15 minutes. Töpfer reagent (dimethylaminoazobenzene that changes color from red to yellow over the pH range of 2.9 to 4.0) is added to ensure the acidity of the specimen. Once collected, two methods can be used to calculate hydrogen concentration. One method involves titrating gastric contents with sodium hydroxide to a pH of 7.0. The amount of sodium hydroxide required will determine the millimoles or milliequivalents of acid collected. Another method uses a pH meter to determine the hydrogen activity of the gastric fluid, which can be used to calculate the concentration of H^+ . The total output of acid by the stomach over an hour is the basal acid output; a normal output is less than 10 mEq/hour for men and 5 mEq/hour for women.



In the past, after the basal acid output had been determined, the maximum acid output could be determined by stimulation with pentagastrin, a synthetic form of gastrin, and measurement of the gastric output. The maximum acid output was often increased in patients with duodenal ulcers. The test is no longer routinely obtained, however, because pentagastrin is not commercially available.

The *bistamine test* is indicated whenever no acid is found in the residual and basal secretions. After the subcutaneous injection of histamine (0.01 mg per kilogram of body weight) or of ametazole hydrochloride (0.5 mg/kg), which is preferred by some authorities because its side effects are less severe, testing for acid continues at 15-minute intervals and is terminated with the first 15-minute specimen in which acid appears. If it has not appeared by the end of 90 minutes, a further attempt to verify the inability to secrete acid is made by the *augmented bistamine test*, in which the injection of a much larger dose of histamine is made possible by the prior administration of an antihistamine drug. (This

procedure is based on the fact that the antihistamines block all but the acid secretory effects of histamine.) Thirty minutes after the administration of the antihistaminic, 0.04 mg/kg of histamine diphosphate is given subcutaneously; the continuously aspirated gastric content is tested at 15-minute intervals with Töpfer reagent. When this reagent, added to the specimens, turns yellow, indicating a hydrogen-ion concentration with a pH above 4.0, it becomes necessary to determine the pH electrometrically with a pH meter before "absolute achlorhydria" can be pronounced.

Gastric analysis, in combination with clinical features and serum gastrin levels, is used in the diagnosis of Zollinger-Ellison syndrome, a hypersecretory disorder characterized by peptic ulceration in the upper intestine distal to the duodenal bulb, multiple endocrinopathies, and secretion of such enormous quantities of HCl as to require total gastrectomy to abolish the ulcerative process. A basal acid output of more than 15 mEq/hour, or more than 5 mEq/hour after stomach surgery, is consistent with a diagnosis of the syndrome.

HELICOBACTER PYLORI INFECTION

Helicobacter pylori is a gram-negative bacteria initially cultured from the human stomach in 1982 and considered the most common cause of gastric mucosal injury. It produces large amounts of urease that protects from acid injury, enabling it to penetrate gastric epithelial cells. The transmission mechanism of *H. pylori* remains unclear. Interpersonal transmission appears to be the main route; transmission by environmental substances, such as contaminated water, is another cause.

The prevalence of *H. pylori* is high in the global population (~50%); it is less frequent in developed areas such as Northern Europe and North America (~30%) compared with Asia and Africa. The worldwide prevalence in the younger generations is declining, mainly in developed countries.

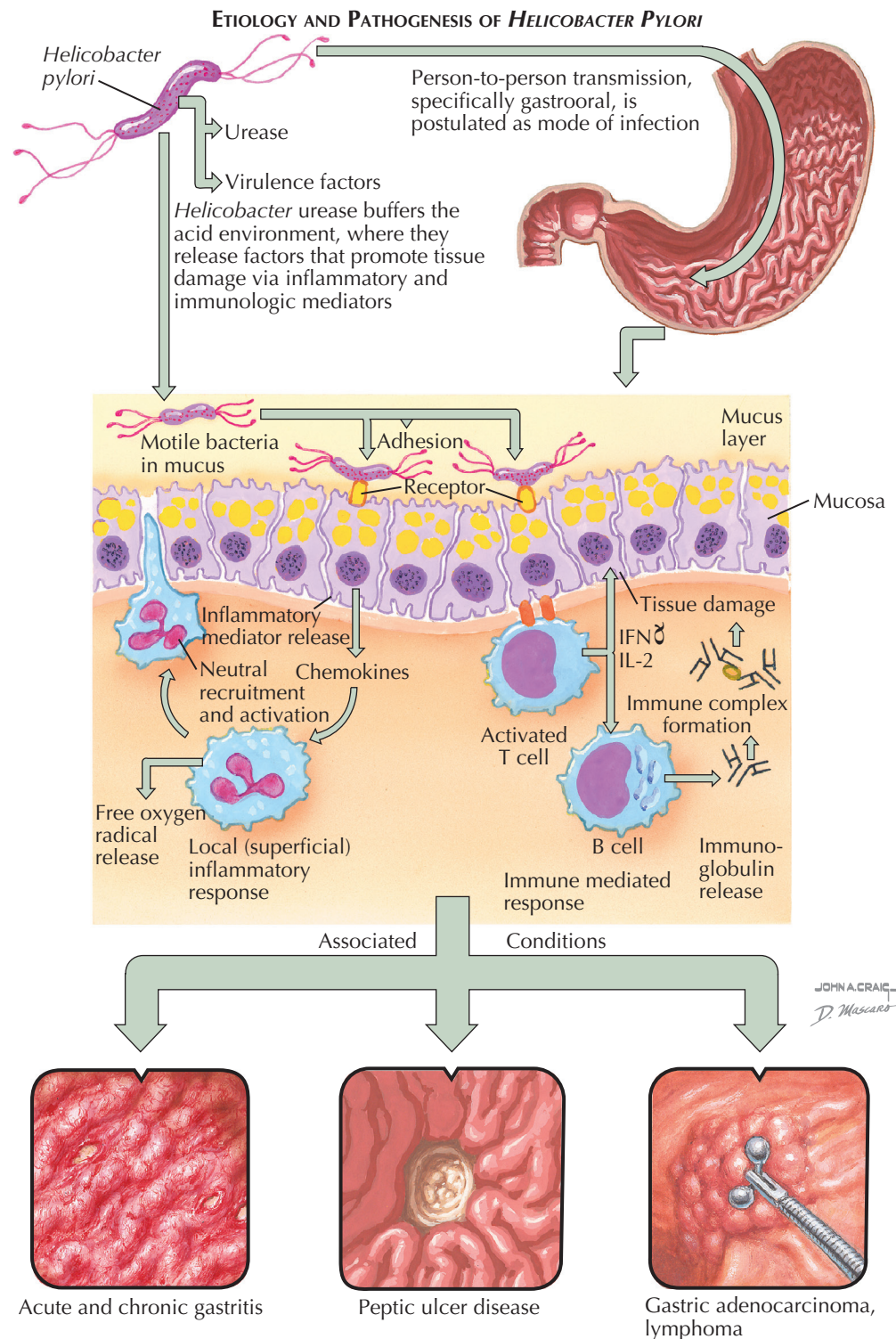
The bacteria causes gastritis; if it persists, gastric atrophy with intestinal metaplasia eventually affects the gastric acid secretion level, based on the location and severity of the inflammation in the stomach. *H. pylori* reduces the mucosal gel layer and affects mucosal blood flow. It is the main cause of duodenal ulcer, through increase in acid pepsin and gastric metaplasia in the duodenal cup. In addition to the host factor and diet, virulence factors of *H. pylori* (CagA, VacA, DupA, IceA, OipA, and BabA) have been revealed to be the predictors of gastric atrophy, intestinal metaplasia, duodenal ulcer, and gastric cancer. However, there is no evidence that strategies based on testing for these factors are useful for an individual patient.

Although *H. pylori* infection does not always cause clinical disease, it strongly affects the relative risk of various disorders in the upper gastrointestinal tract, such as gastritis, peptic ulcer disease, gastric cancer, MALT lymphoma, idiopathic thrombocytopenic purpura, and iron deficiency anemia. On average, the *H. pylori* status has no effect on symptom severity, recurrence, or treatment efficacy in patients with GERD. Many patients have functional dyspepsia symptoms rather than peptic ulcer disease.

Endoscopic biopsies enable culture and histologic examination with excellent results. The rapid urease test and polymerase chain reaction procedure for gastric biopsy specimens also have a high yield. The noninvasive C13-urea breath test and stool antigen test have high sensitivity and specificity, and both tests are recommended for detection. However, proton pump inhibitors and antibiotic treatment can affect and inhibit urease activity. Serologic results for anti-*H. pylori* antibodies are not all equivalent, and only validated immunoglobulin G serology tests should be used owing to variability in different commercial tests.

H. pylori infection is the most consistent risk factor for gastric cancer. Its elimination is the most promising strategy for reducing the incidence of gastric cancer and lowering the risk of recurrent peptic ulcer bleeding. Guidelines therefore advocate a test-and-treat strategy for patients with a history of ulcer bleeding and NSAID and/or aspirin use.

The first-line treatment is a proton pump inhibitor combined with clarithromycin and amoxicillin for 10 to 14 days. Regimens containing clarithromycin are the first-line treatment only in areas of low clarithromycin resistance ($\leq 20\%$). Regimens containing four agents, including bismuth, are alternative first-line treatments. If this regimen is not available, sequential treatment or a four-agent regimen not containing bismuth is recommended. If proton pump inhibitor-clarithromycin

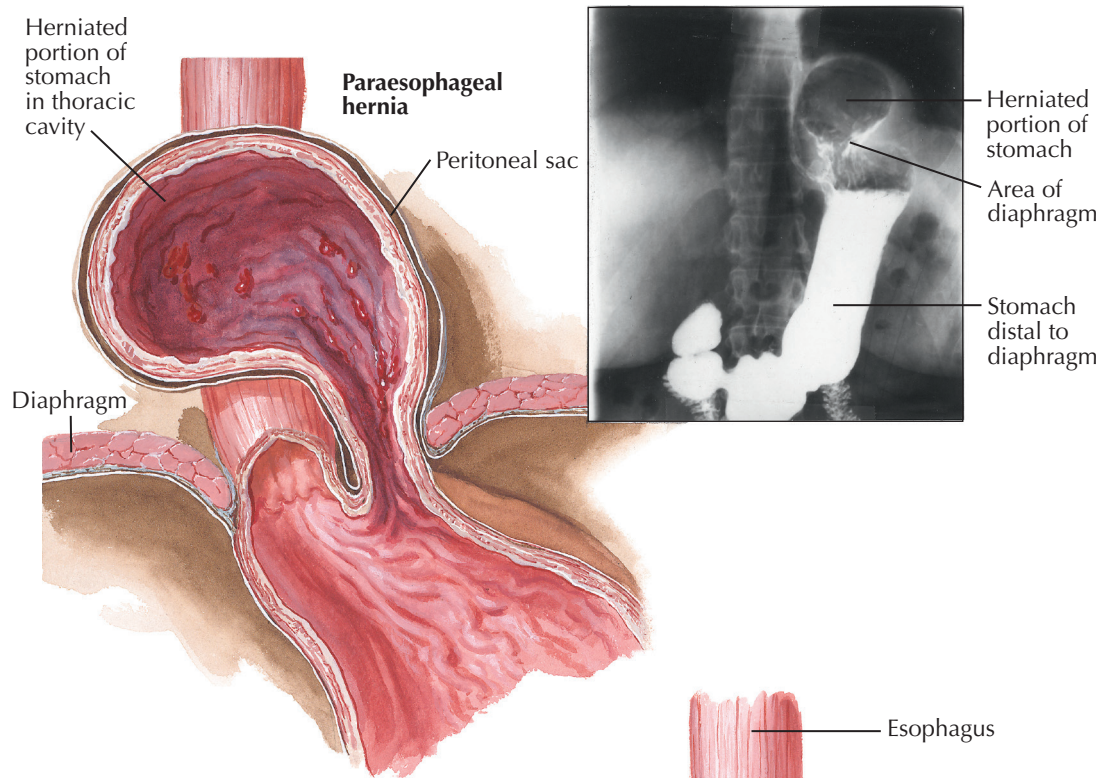


therapy fails, either four-agent therapy including bismuth or three-agent therapy containing levofloxacin is recommended (rising rates of levofloxacin resistance should be taken into account, however). Choosing a third-line regimen should be guided by antimicrobial susceptibility testing whenever possible.

Confirmation of eradication is recommended at least 4 weeks after treatment. A urea breath test or monoclonal stool test is recommended as a noninvasive test for determining eradication success; currently, there is no role for serologic testing. In countries where *H. pylori* infection is prevalent, studies focusing on virulence factors and antibiotic susceptibility may improve

the prognosis and be helpful in reducing complications and the risk of death.

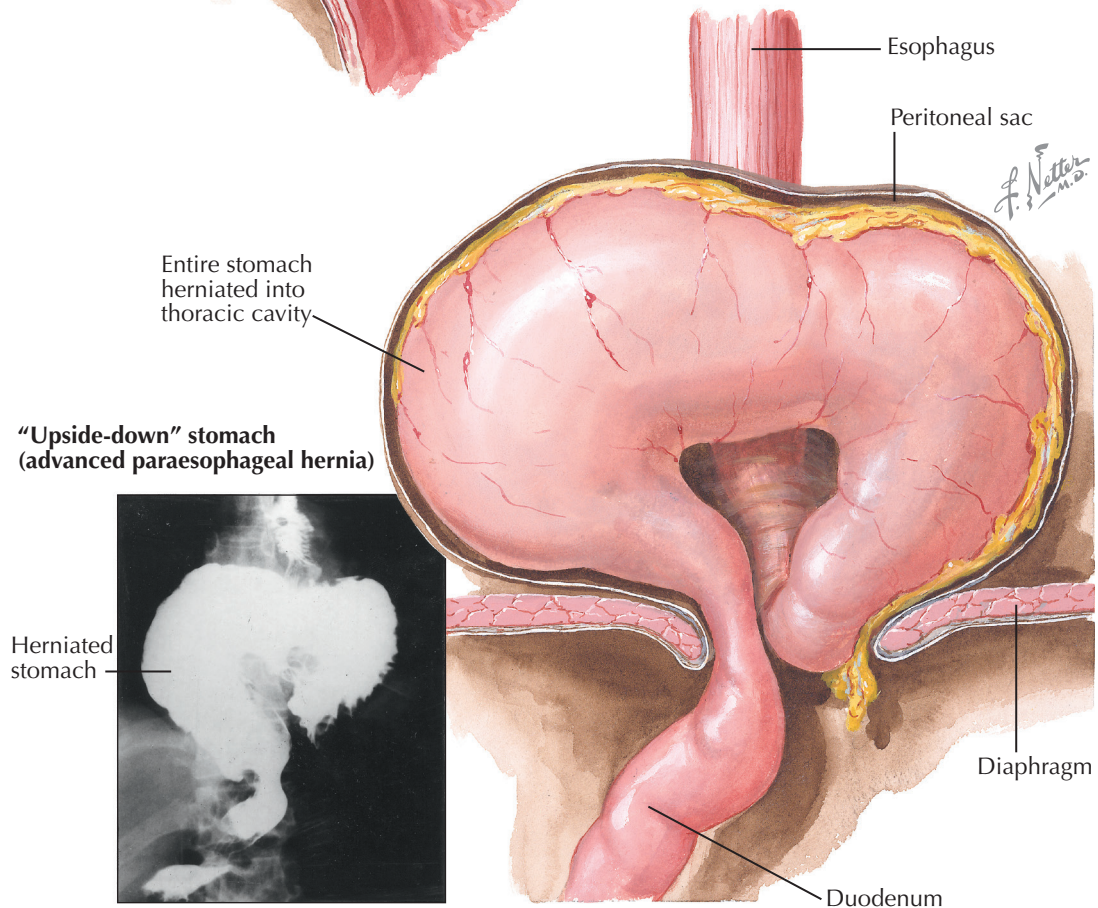
H. pylori posteradication recurrence is infrequent and is found mainly in areas of low socioeconomic development. Eradication reduces the risk of complicated and uncomplicated peptic ulcer disease associated with use of NSAIDs or low-dose acetylsalicylic acid. *H. pylori* eradication is beneficial before starting NSAID treatment, and mandatory in patients with a history of peptic ulcer disease. Eradication produces long-term relief of dyspepsia in 1 of 12 patients with functional dyspepsia, a rate that is better than for any other treatment available.



PARAESOPHAGEAL HERNIA AND GASTRIC VOLVULUS

A paracardial or *paraesophageal hernia* is seen less frequently than is a sliding diaphragmatic hernia and is characterized by the protrusion of the gastric fundus into the intrathoracic space alongside the esophagus, which is of normal length and in the usual and fixed position. The cardia and its attachment by the gastro-phrenic ligament remains intact while the fundus slips through a fibromuscular defect directly to the left or right of the gastroesophageal junction. The parietal peritoneum, which normally covers the abdominal surface of the diaphragm, has prolapses and serves as the outer wall of the *hernia sac*. These anatomic relations explain why, with a paraesophageal hernia, there is no insufficiency of the lower esophageal sphincter mechanism and, hence, no occurrence of peptic esophagitis.

The hiatus between the terminal portion of the esophagus and the diaphragmatic crus (or phreno-esophageal ligament) is, as a rule, so narrow that it may interfere with the circulation of the prolapsed portion of the fundus, which will consequently become congested. The venous congestion leads to inflammatory reactions of the mucosa, which tends then to erode or bleed, particularly in the area of the hiatal defect. The resulting blood loss, in some cases, may be of such magnitude as to produce a chronic and recurrent anemia, which may be the first and only clinical sign of the disease. The paraesophageal hernia, however, assumes its clinical significance essentially by the potential danger of strangulation of the herniated parts. The predominant symptoms with this type of hernia are epigastric and substernal pain, nausea, and, rarely, dysphagia. An increase in the intermittent attacks of pain, the appearance of hematemesis, and a tendency toward cardiovascular collapse should always arouse the suspicion of a possible strangulation. Careful examination of a chest radiograph may reveal a gas bubble from the



herniated gastric fundus adjacent to the normally placed esophagus with normal topographic relations of the gastroesophageal junction.

An extreme variant of the paraesophageal hernia has been quite pertinently called the *upside-down stomach*. In such instances a markedly widened hiatus in the diaphragm has permitted the entire stomach to enter the thorax and lie within the herniated sac. The stomach is rotated around its longitudinal axis, and the more

movable major curvature thus becomes the dome of the prolapse. The cardia and pylorus are in close apposition to each other, and lie, with such a complete herniation of the organ, at the same level.

Once the diagnosis of a paraesophageal hernia has been established, its surgical repair is definitely indicated, not only because of the symptoms and signs (epigastric pain and anemia) but more so because of the always imminent danger of incarceration.

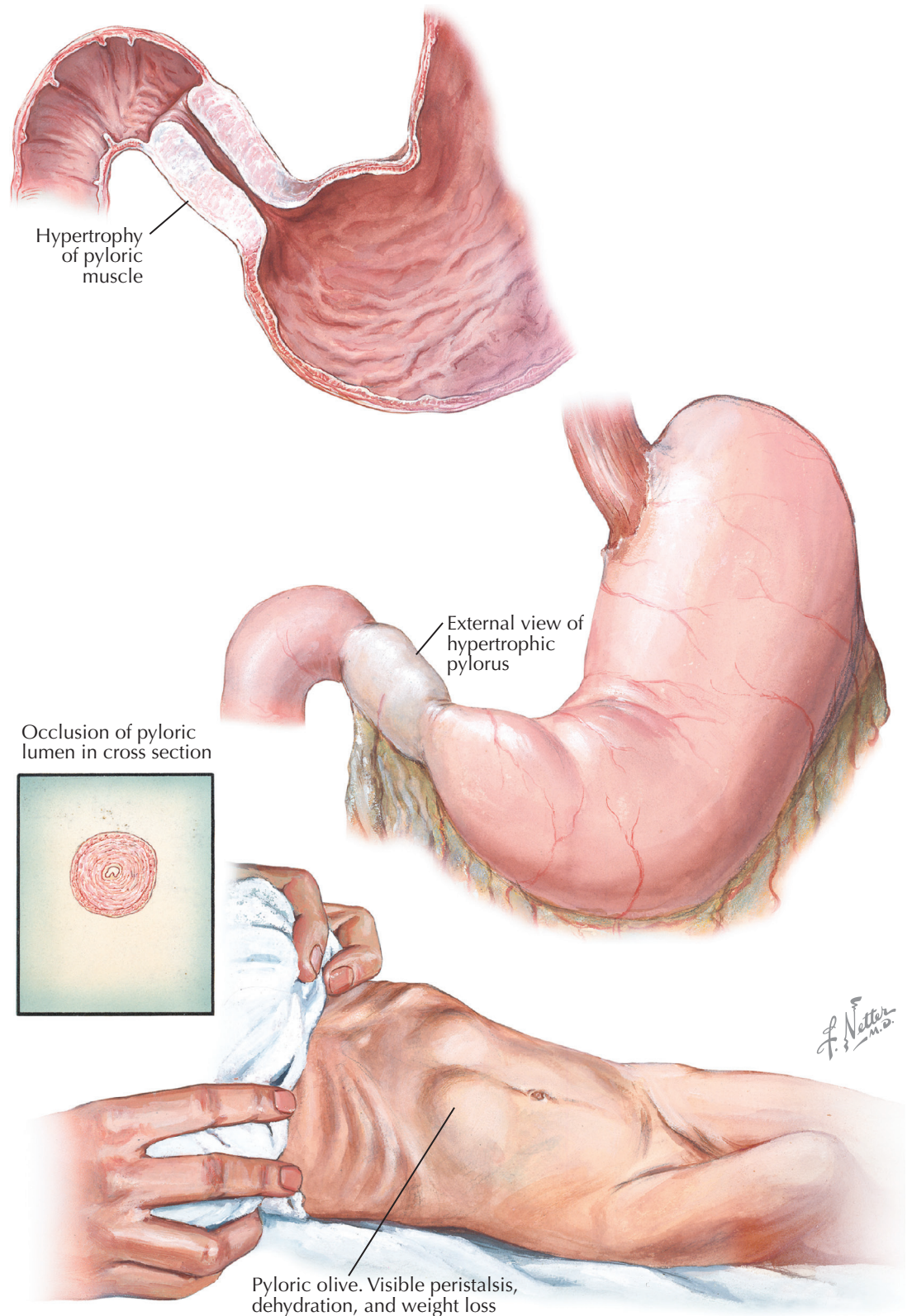
HYPERTROPHIC PYLORIC STENOSIS

Hypertrophic pyloric stenosis is predominately a neonatal disorder. Its exact cause and pathogenesis remain debated. It may be due to a lack of localized nitric oxide synthase, which normally allows for smooth muscle relaxation. It is unknown if the lack of nitric oxide synthase is a primary or secondary event, as it is not seen in all cases. In hypertrophic pyloric stenosis, the interstitial cells of Cajal, which are the pacemaker cells of the gastrointestinal tract, are only seen near the submucosa rather than throughout the entire pylorus. Epidermal growth factors (EGFs), their receptors, and heparin-binding EGF-like growth factors are also increased in smooth muscle cells in hypertrophic pyloric stenosis, but the trigger for these increased growth factors remains unknown.

The term *hypertrophic pyloric stenosis* is a misnomer, because the disorder is not due to hypertrophy but rather to hyperplasia of the smooth muscle layers of the prepyloric region, particularly the circular layer. The increase in muscular mass *diminishes the size of the lumen*, causing obstruction. Depending upon the degree of the obstruction and its duration, the stomach may be enormously dilated. The *pylorus* bulges forward like a tumor, terminating abruptly at the beginning of the duodenum at one end and, on average, about 2 cm proximally at the other end. The consistency of the pylorus in this condition is remarkably firm, almost as hard as that of cartilage. The condition occurs five to seven times more frequently in boys than in girls and occurs in about 3 in 1000 live births. It is more common in those of Northern European descent.

Vomiting is classically the first symptom and may appear between the second and sixth weeks of life. It may begin with mild spitting, but increases in frequency and severity that progresses to projectile vomiting. The infants cry, indicating hunger and willingness to take food. With less food and fluid passing through the obstructed pylorus, the *patients* lose weight and become *dehydrated*. In this stage a metabolic alkalosis may present a serious problem. The enlarged pylorus may be palpated as the classic “olive,” and strong peristaltic movements of the stomach may be observed on simple inspection of the abdominal wall. Adults typically present with nausea, vomiting, early satiety, and postprandial epigastric pain. The enlarged pylorus is less readily palpable on the adult physical examination.

Diagnosis in infants can often be made by the history and physical examination. X-ray examination may be done prior to surgical repair. On a barium study, the stomach appears abnormally large and dilated, with no passage of contrast in the duodenum until $\frac{1}{2}$ hour to 2 hours later. Diagnosis can be confirmed using abdominal ultrasound, which will show a hypertrophied canal that appears as a sonolucent 3-mm “doughnut.” In



adults, upper endoscopy is recommended to rule out chronic peptic or malignant disease.

Treatment for hypertrophic pyloric stenosis begins with fluid resuscitation and correction of electrolyte abnormalities. Medical therapy with anticholinergics has a high failure rate, and is therefore rarely used. Definitive treatment is with Ramstedt pyloromyotomy, where a longitudinal incision is made through the hypertrophied muscle down to the submucosa. An alternative surgery is pyloric trauma myoplasty, where

the pylorus is grasped with a Babcock clamp, causing displaced muscle at two locations. Laparoscopic pyloromyotomy has become increasingly common. Infants resume normal growth and development after pyloromyotomy. The resulting cure is permanent, leaving no tendency to diseases of the upper gastrointestinal tract. In adults, resection of the pylorus is recommended to rule out malignancy. The pylorus can also be endoscopically dilated, but this is associated with a higher failure rate.

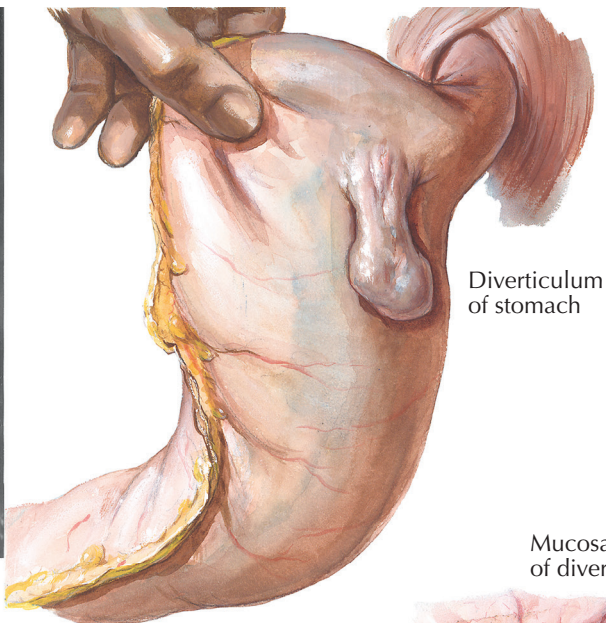
DIVERTICULUM OF STOMACH; GASTRODUODENAL PROLAPSE

Gastric diverticulum is an outpouching of the gastric wall. Gastric diverticula are rare, and they are commonly detected incidentally during routine diagnostic testing, such as upper endoscopy and upper gastrointestinal radiologic study. These *diverticula of the stomach* are often of little practical significance, but they may be worth considering in a differential diagnosis. Most gastric diverticula are asymptomatic, but they may present with a vague sensation of fullness or discomfort in the upper abdomen. The presenting complaint might also be the result of a complication of a gastric diverticulum, such as acute upper gastrointestinal bleeding or perforation.

Gastric diverticula are practically all located on the posterior wall of the cardia and to the left of the esophagus. Diverticula located at the pyloric end of the stomach or on the anterior wall of the cardia have been reported only in a few isolated cases. Whether gastric diverticula develop in postnatal life or originate during the fetal period cannot be decided upon with certainty. Small sacculations of the posterior wall have occasionally been observed in the stomach of the human fetus. On the other hand, the structural weakness of the longitudinal muscles on the posterior surface points also to the possibility that the diverticula may be acquired during a lifetime by a pulsion mechanism. Both theories could explain the site of predilection and the rare occurrence of diverticula.

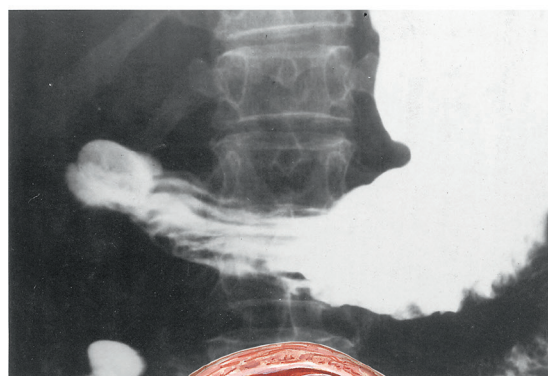
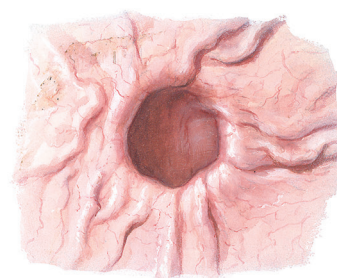
As a rule, all layers of the stomach participate in forming the pouch of the gastric diverticula, but, occasionally, one or the other layer may be absent totally or in part. The diverticula are usually 2 to 3 cm long and from 1 to 2 cm in diameter. The opening of the diverticulum is, in most cases, wide enough to allow free communication between the pouch and the stomach, and these patients have no complaints. Occasionally, the ingesta may become impacted and cause inflammation. The danger of a perforation is relatively small. *Roentgenographically*, a diverticulum of the stomach may be demonstrated as a saccular structure that fills with barium when the patient is asked to lie down and, a few minutes later, to stand up. The pouch on the posterior wall may be seen within the cardiac air bubble at some distance to the left of the esophageal entrance. Overdistention of the stomach with barium may obscure the deformity. Sometimes it may be necessary to turn the patient obliquely, with the right side against the screen or film. The diverticulum will then appear to extend from the lesser curvature. A penetrating ulcer in the upper regions of the stomach may produce x-ray pictures quite similar to those of a diverticulum, and if the clinical manifestations are very pronounced, it is preferable to assume the presence of an ulcer.

A *prolapse of the gastric mucosa into the duodenum* probably develops because of extreme movability of the antral mucosa and submucosa, which, for one reason or

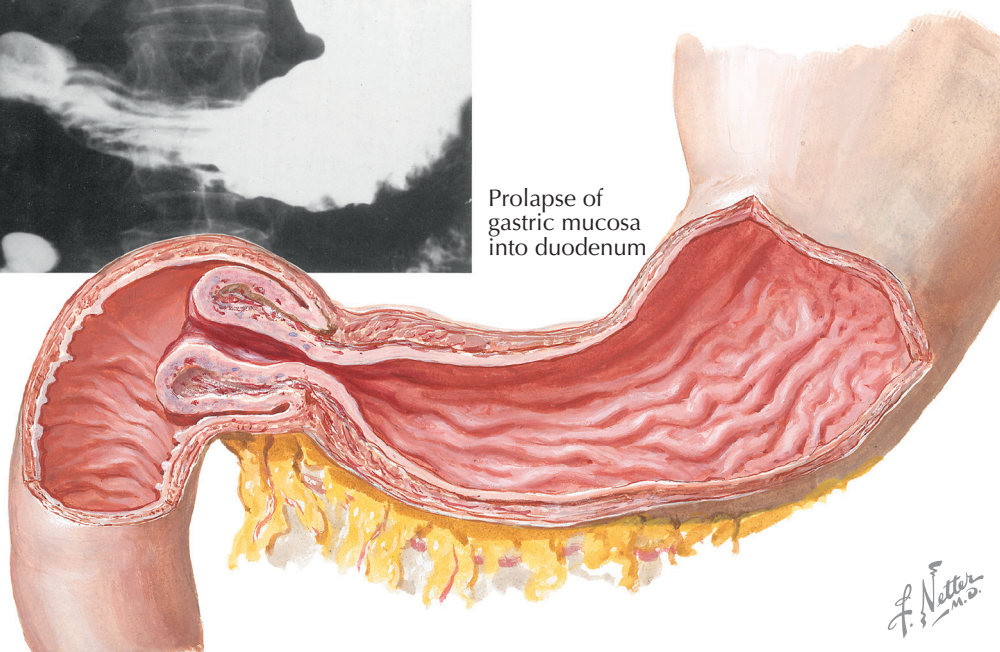


Diverticulum
of stomach

Mucosal aspect
of diverticulum



Prolapse of
gastric mucosa
into duodenum



another, adhere only loosely to the external layers of the wall. The mucosa of the antrum, which normally is thicker than the mucosa of other parts of the stomach and sometimes assumes a cushionlike quality, is pushed through the pyloric ring to lie like a turned-back cuff of a sleeve within the duodenum. A fully developed prolapse is rare, but partial ones are quite frequent, though they have little or no clinical significance. In the *x-ray picture* the bulb of the duodenum appears as if it were filled with a tuberous mass, which has irregular

contours owing to the fact that the contrast medium lies only on top of the mucosal folds and is absent in the pits. The diagnosis is easy, thanks to the typical configuration, and in only a few special cases is it difficult to differentiate such a prolapse from a polyp or an acute ulcer with a marked mucosal edema of its surroundings. Strangulation of the prolapsed segment and extreme swelling of the mucosa, with subsequent signs of a pyloric stenosis or hemorrhages from congested mucosal blood vessels, are rare occurrences.

TRAUMATIC INJURIES OF THE STOMACH

Abdominal trauma can cause serious injury to the stomach, small bowel, and colon. The nature and severity of the injury depend upon whether the injury mechanism is blunt or penetrating.

Blunt gastrointestinal injury may result in crushing of the bowel between the body's solid structures, such as the spine or pelvis, and an external blunt force, such as a steering wheel, seatbelt, or handlebar. Blunt gastrointestinal injury occurs more commonly in the small bowel, followed by the colon and then the stomach. Rupture of the stomach is relatively uncommon because of the stomach's relatively protected anatomic location.

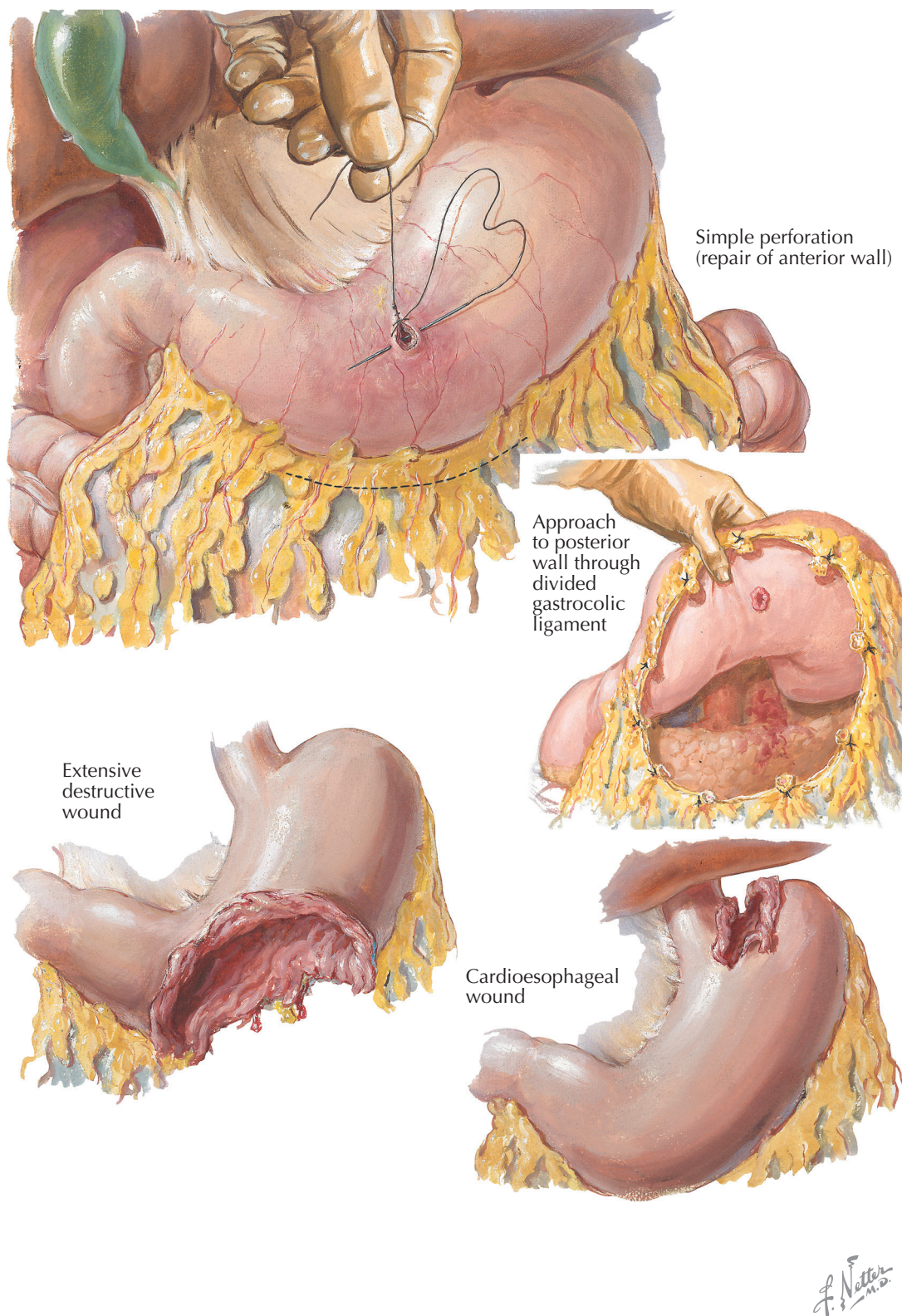
Injuries of the stomach occur relatively frequently with any penetrating or perforating wound of the abdomen, as can occur with gunshots and knife stabbings. According to statistical data of war surgery, about 8% of abdominal wounds involve the stomach, and in approximately 5% the stomach alone is injured. With blunt trauma to the upper abdominal region, the stomach may become lacerated, or it may even rupture if the organ is filled and distended at the moment of impact.

The type of gastric wound produced by a bullet or sharp instrument depends upon the size, shape, course, and velocity of the wounding agent. Bullets that enter from the front, taking an anteroposterior course, often cause only small perforations of the wall. Larger shell fragments can produce rather *extensive jagged lacerations*, which may completely sever the stomach from the duodenum, particularly if they include the gastric antrum. *Wounds of the cardia* often involve the lower end of the *esophagus* and *mediastinum*.

The clinical manifestations of any perforating injury of the stomach are often very dramatic. Depending upon the size of the wound, the loss of blood, and the presence or absence of concomitant injuries, either shock or signs of peritonitis dominate the clinical picture. Small perforations, causing little shock, may first cause localized and then diffuse pain, which is soon followed by rigidity of the abdominal wall, nausea, and vomiting of bloody material. The entry of air into the abdominal cavity can be demonstrated radiologically. Small *perforating injuries of the cardia* produce, in the beginning, very few or no clinical symptoms. In most cases only left shoulder pain due to an inflammatory reaction of the diaphragmatic peritoneum is present.

The prognosis of any gastric wound depends upon the promptness of appropriate treatment, which is primarily surgical intervention, rather than upon the type and degree of the injury. In World War I, the mortality rate for all gastric wounds ranged between 50% and 60%, owing to the frequency of hemorrhagic shock and peritoneal infection, and the rate for uncomplicated wounds restricted to the stomach ranged between 25% and 50%. Much progress has been made since then in treating shock and infection, including improved access to medical care with trauma centers, resulting in a tremendous reduction in these mortality figures.

Treatment for injuries of the stomach is primarily surgical, done at the earliest possible time. With both gunshot and stab wounds, the *posterior* as well as the *anterior wall* may be *injured* simultaneously, so that it



becomes obligatory to explore the posterior wall in every instance by adequately detaching the gastrocolic ligament and pulling the stomach upward. Cases in which the anterior gastric wall has remained intact and the posterior wall alone has been perforated, even though the shot or puncturing instrument entered through the anterior abdominal wall, have been reported. This can happen if, at the time of the accident, the stomach was so tightly filled that the greater curvature, rotating around the longitudinal axis of the stomach, has turned forward and upward. In this

position the inferior aspect of the posterior wall approaches the anterior abdominal wall.

Extensive destructive wounds, with major defects of the stomach, cannot be repaired and make a typical gastrectomy or removal of large parts of the stomach inevitable.

If the cardia has been injured, a left thoracotomy becomes necessary in order to ensure a sufficient view and also freedom of action to perform a gastroesophageal resection in instances in which the esophagus also is found to be involved.

GASTRITIS

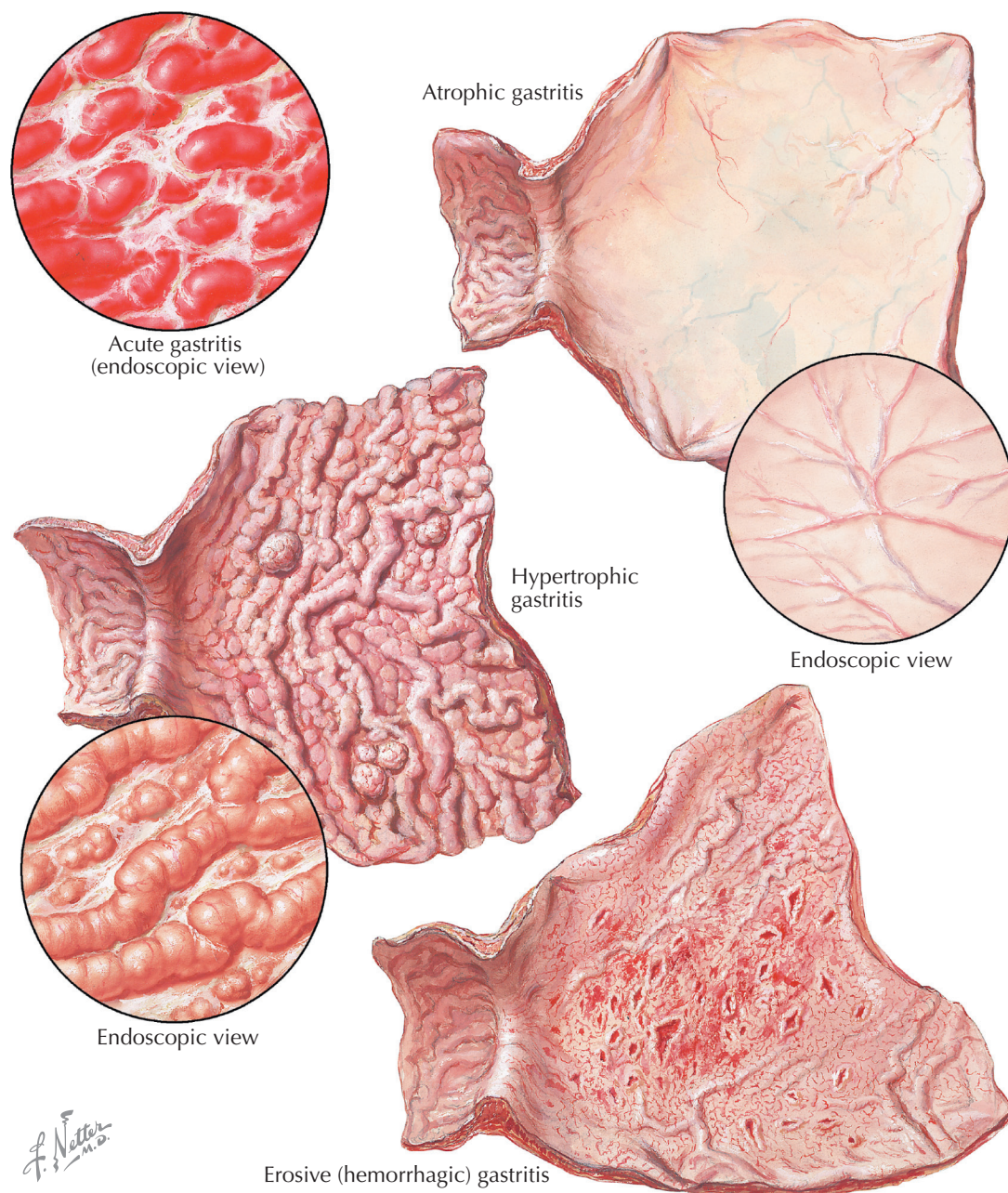
Gastritis is an inflammation of the mucosal lining of the stomach. It can occur suddenly (acute) or gradually (chronic). Gastritis can be caused by irritation or inflammation from excessive alcohol use or the use of certain medications such as aspirin or other antiinflammatory drugs. It may also be caused by *H. pylori* and other bacterial and viral infections, pernicious anemia, and bile reflux.

Gastric irritation from abuse of alcohol, coffee, and tobacco and from chemicals and drugs such as NSAIDs and, perhaps, corticosteroids is the main cause of *acute gastritis*. Acute gastritis may also develop during many febrile infections, such as typhoid, pneumonia, and diphtheria. *H. pylori* infection can present with acute gastritis. The gastric mucosa in acute gastritis is erythematous, often with erosions, and may be covered with a thick mucus. Symptoms of gastritis vary among individuals, and in many people there are no symptoms. The most common symptoms include epigastric pain or discomfort, nausea or indigestion, vomiting, a burning or gnawing feeling in the stomach between meals or at night, and a disagreeable taste. A corrosive type of gastritis, originating from the intake of strong chemicals such as lye, can lead to a localized or diffuse necrosis and permanent scarring.

Erosive hemorrhagic gastritis is characterized by multiple, diffuse erosions in an inflamed mucosa. Nausea, anorexia, pain, and gastric hemorrhage may occur. This acquires a special clinical significance with its tendency to cause severe, at times life-endangering, hemorrhages. Larger arteries extend quite frequently as far up as the epithelium and may become involved in some of the many small, but by no means superficial, erosions. Whenever the origin of gastrointestinal bleeding cannot be identified, the possibility of an erosive hemorrhagic gastritis must be seriously considered, especially in severely ill hospitalized patients. Endoscopy is important for the diagnosis, though during an episode of acute bleeding the mucosa may not be well visualized. At laparotomy the diagnosis may still be difficult, because, even when viewing the mucosa directly after gastrotomy, the small erosions (i.e., the source of the bleeding) may not be well seen macroscopically.

A similar type of hemorrhagic gastritis has been observed after partial resection of the stomach or after gastroenterostomy or ulcer. This should be kept in mind if the suspicion of a bleeding peptic "anastomotic ulcer" cannot be confirmed unequivocally by x-ray studies, endoscopically, or at laparotomy. Under such circumstances, vagotomy may be the best procedure to stop the bleeding. It has helped in many cases and, in any event, is preferable to an additional resection.

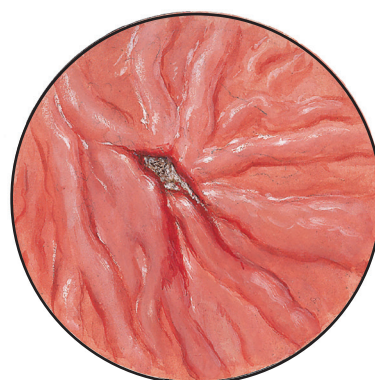
Chronic atrophic gastritis is a process of chronic inflammation of the stomach mucosa, leading to loss of gastric glandular cells and their eventual replacement by intestinal and fibrous tissues. This may be an aftermath of



an acute gastritis, but many other possible etiologic factors of exogenous or endogenous origin need to be considered. Chronic atrophic gastritis has a close relationship to pernicious anemia and vitamin B₁₂ deficiency. The relationship of chronic atrophic gastritis and, more specifically, pernicious anemia with malignancies has not been clarified. The characteristic features of chronic atrophic gastritis endoscopically are the disappearance of the folds and the thinness of the mucosa through which shines the vascular net, both arterial and venous. Microscopically, the chief and parietal cells are considerably reduced in size and number; the epithelial cells are transformed to a great extent into goblet cells, or undergo metaplastic changes. The clinical manifestations are rather nonspecific. Upper endoscopy with biopsies of the gastric body is used to establish the diagnosis.

With chronic *hypertrophic gastritis* the situation is clinically much the same, except that hyperacidity is present in most cases, and the distribution of the rugae

and the "cobblestone" appearance of the mucosal surface, seen roentgenographically, provide more often the right clue for diagnosis; endoscopy is needed to make the unequivocal diagnosis. The rugae are strikingly thickened and, even at autopsy, do not flatten out when the wall is stretched. *Ménétrier disease* (also known as hypoproteinemic hypertrophic gastropathy) is a rare, acquired disorder of the stomach characterized by greatly thickened gastric folds and excessive mucus production, with resultant protein loss leading to diarrhea. Other conditions, such as lymphoma and Zollinger-Ellison syndrome, can cause hypertrophic mucosal folds in the stomach, and use of proton pump inhibitors can also be a cause. In Zollinger-Ellison syndrome, or gastrinoma, the elevated serum gastrin levels lead to parietal cell hypertrophy, prominently in the fundus and body of the stomach. The use of proton pump inhibitors results in gastric hypoacidity leading to increases in gastrin levels and, also, parietal cell hypertrophy.



Acute gastric ulcer
(endoscopic view)

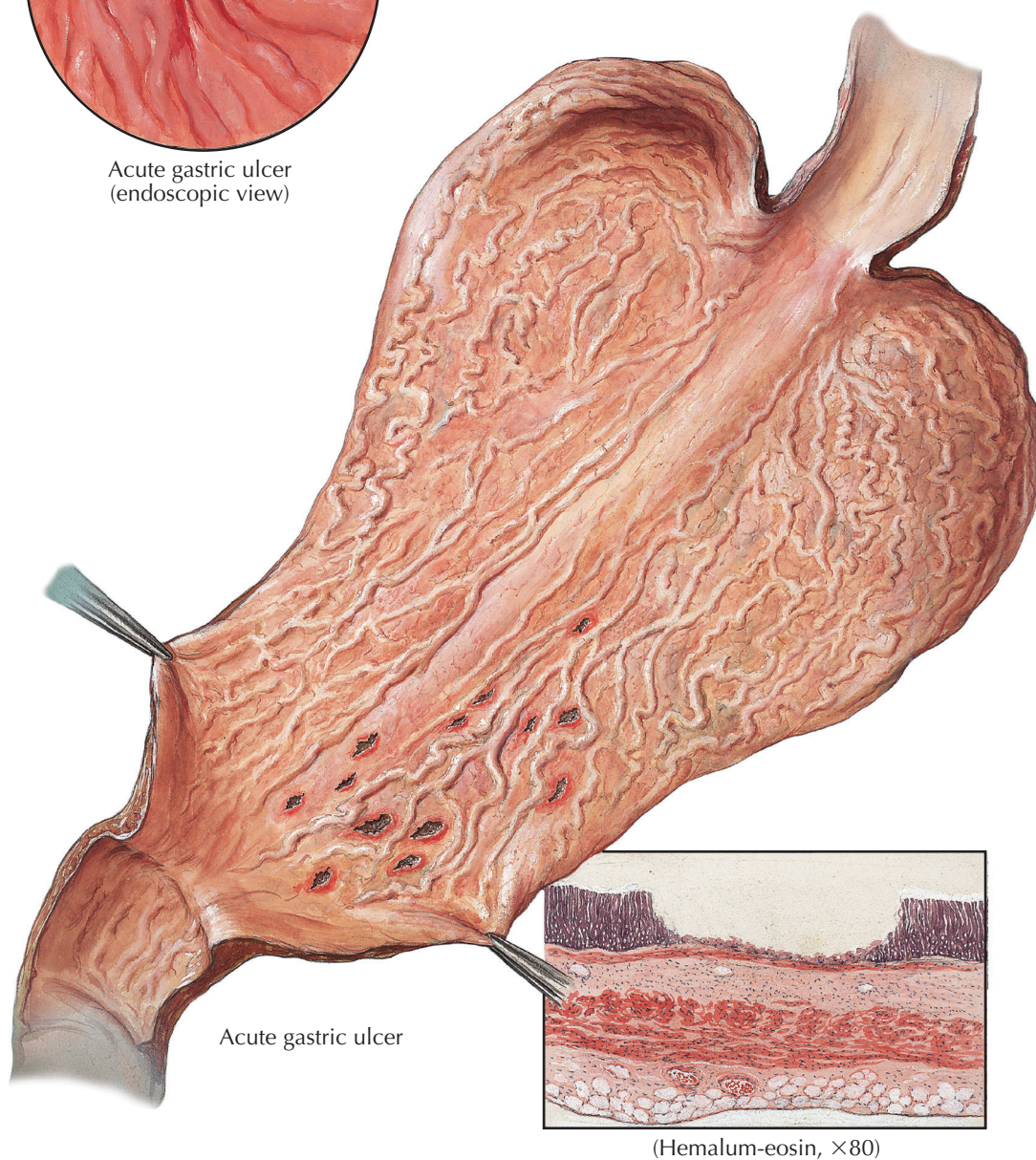
ACUTE GASTRIC ULCER

The cause of gastric or duodenal ulcers was a matter of debate during several decades; there are now known to be two main causes. *H. pylori* infection is a factor in many peptic ulcers, both gastric and duodenal; its causative role appears to be decreasing, however. Aspirin and other NSAIDs are also a known cause of gastric ulcers. A significant minority of these ulcers have causes other than *H. pylori* infection or NSAID use.

Small superficial erosions of the gastric mucosa, even those with a tendency to bleed, may cause few or no symptoms, though they are noted quite often by the endoscopist. *Acute ulcers* are characterized by a somewhat greater defect of the mucosa and sometimes of the uppermost stratum of the submucosa. Their size varies considerably between the extremes of a few millimeters to 3 to 4 cm. Acute ulcers are usually multiple; the greater their number, the smaller their size. Single acute ulcers are rare. The site of predilection for acute ulcers is the prepyloric region, but occasionally very small ones may arise in the mucosa of the body and along the greater curvature. In contrast, larger acute ulcers are sometimes found along the so-called *Magenstrasse*, a groove along the lesser curvature that is the route food and liquids tend to take in moving toward the pylorus.

In its earliest stages, an acute ulcer appears as a shallow necrotic region, with a slightly raised soft margin surrounded by tissue which may or may not show a mild inflammatory reaction. The floor of the ulcer can appear black, as a consequence of the chemical changes produced by the hydrochloric acid on the blood that oozes from the lesion. At times the bleeding may be more pronounced, or even severe, with a relatively small ulcer. Should the ulcerative process reach the muscularis mucosae, this layer retracts, drawing the edges of the ulcer downward in opposition to each other. The original shape of the acute ulcer is oval, but it assumes a slitlike shape when the stomach wall contracts.

Although it is generally agreed that acute ulcers may become subacute or chronic, as a rule they have a good and relatively rapid healing tendency. The healing process starts with growth of the epithelium from the margins across the area from which the necrotic parts have been sloughed. From the newly formed epithelium, the growth is downward. Even the muscularis mucosae, if involved in the process, may be completely restored.



Acute gastric ulcer

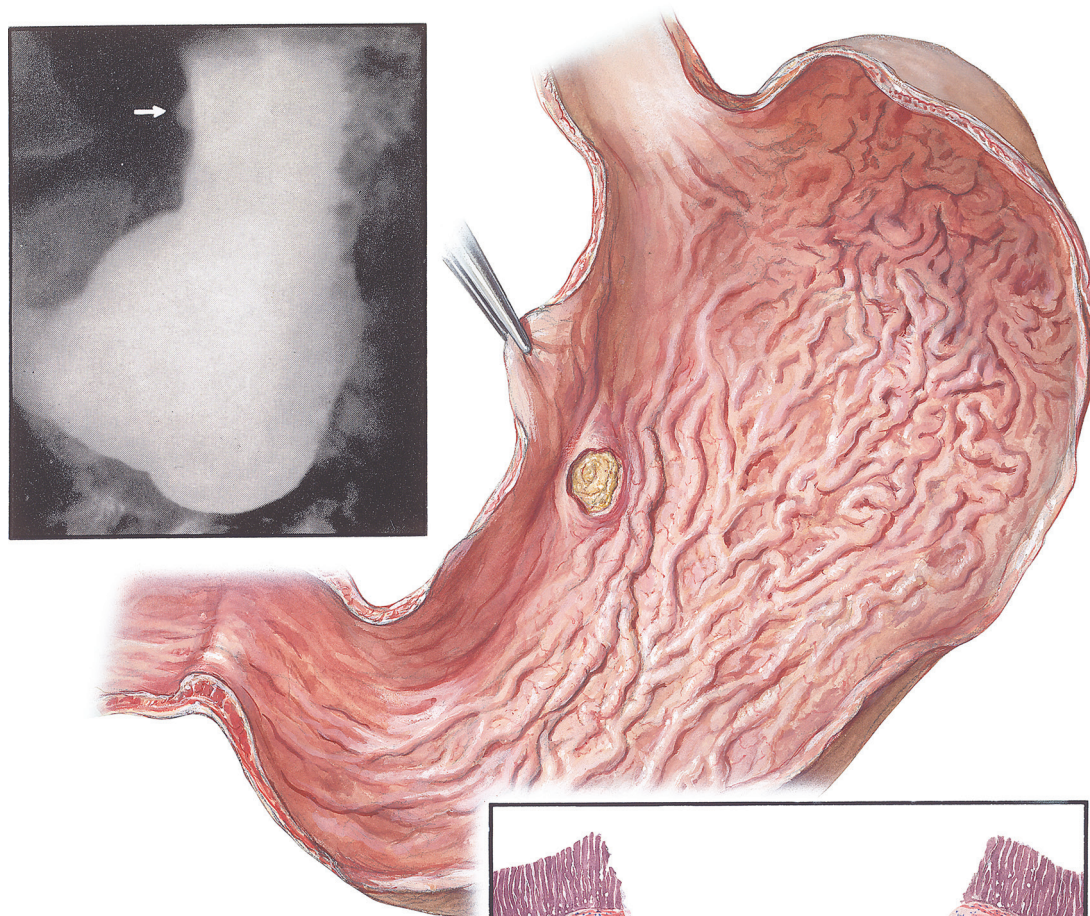
(Hemalum-eosin, $\times 80$)

The diagnosis of an acute ulcer is not often made on clinical grounds, except when *endoscopy* is employed. The symptoms, if any, are negligible and certainly less pronounced than with an acute diffuse gastritis.

A special type of acute peptic ulcer of the stomach or duodenum, the so-called *stress ulcer*, has been discussed widely; its pathophysiologic relationship has not yet been completely clarified. It may develop following extensive burns (Curling ulcer), in the course of tetanus, after brain surgery (Cushing ulcer), or in the course of

therapy with corticosteroids (steroid ulcer) or NSAIDs. The specific features of this ulcer type are the rapidity with which it comes into existence, the lack of any inflammatory reaction around the ulcer, complete absence of pain, and a pronounced tendency to perforation and bleeding. The frequency of ulcer formation during steroid therapy, however, has been controversial, with recent studies showing only a marginal increase in ulcer formation in patients receiving steroid treatment.

F. Netter M.D.



SUBACUTE ULCER OF STOMACH

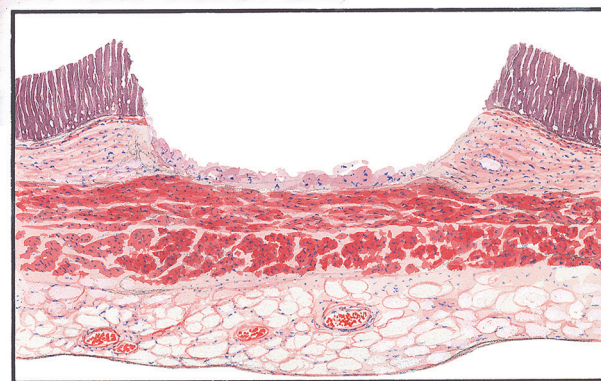
An ulcer in the transitional stage between acute and chronic has been termed *subacute ulcer*. Morphologically, it differs in degree from an acute ulcer insofar as it is more rounded and has a greater depth. Its walls are thicker and higher, and its shape is occasionally funnel-like, with irregular contours. The subacute phase of a peptic ulcer has *involved both the mucosa and submucosa*, but at times it may reach the muscular coat. In any event, the subacute ulcer may have the same potential danger for perforation or profuse bleeding as does an acute or a chronic ulcer. At the *floor of the ulcer*, one finds purulent, grayish-yellow, necrotic material. The grayish-white color on the floor or edges may be due also to proliferating fibroblasts, as a token of a healing tendency and the beginning of scar formation.

Only one subacute ulcer is usually present. If multiple subacute ulcers are present, they are larger than single or multiple acute ulcers, though, as a rule, smaller than a fully developed chronic lesion would be.

The concept of the subacute ulcer is derived essentially from observations of the pathologist. In view of the enormous variability in the size, shape, depth, and other features characteristic of any transitional stage or form of the pathologic process, the term cannot be sharply defined. Clinically, it is almost impossible to commit oneself definitely to the diagnosis of subacute ulcer, except occasionally, when the duration of the

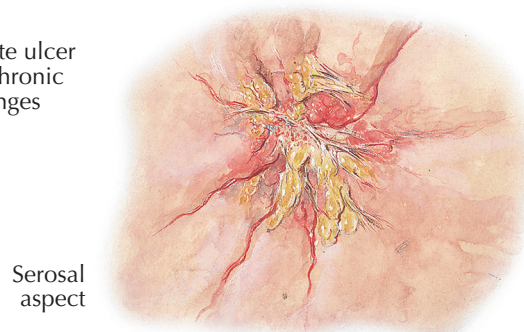


Mucosal aspect



Subacute ulcer

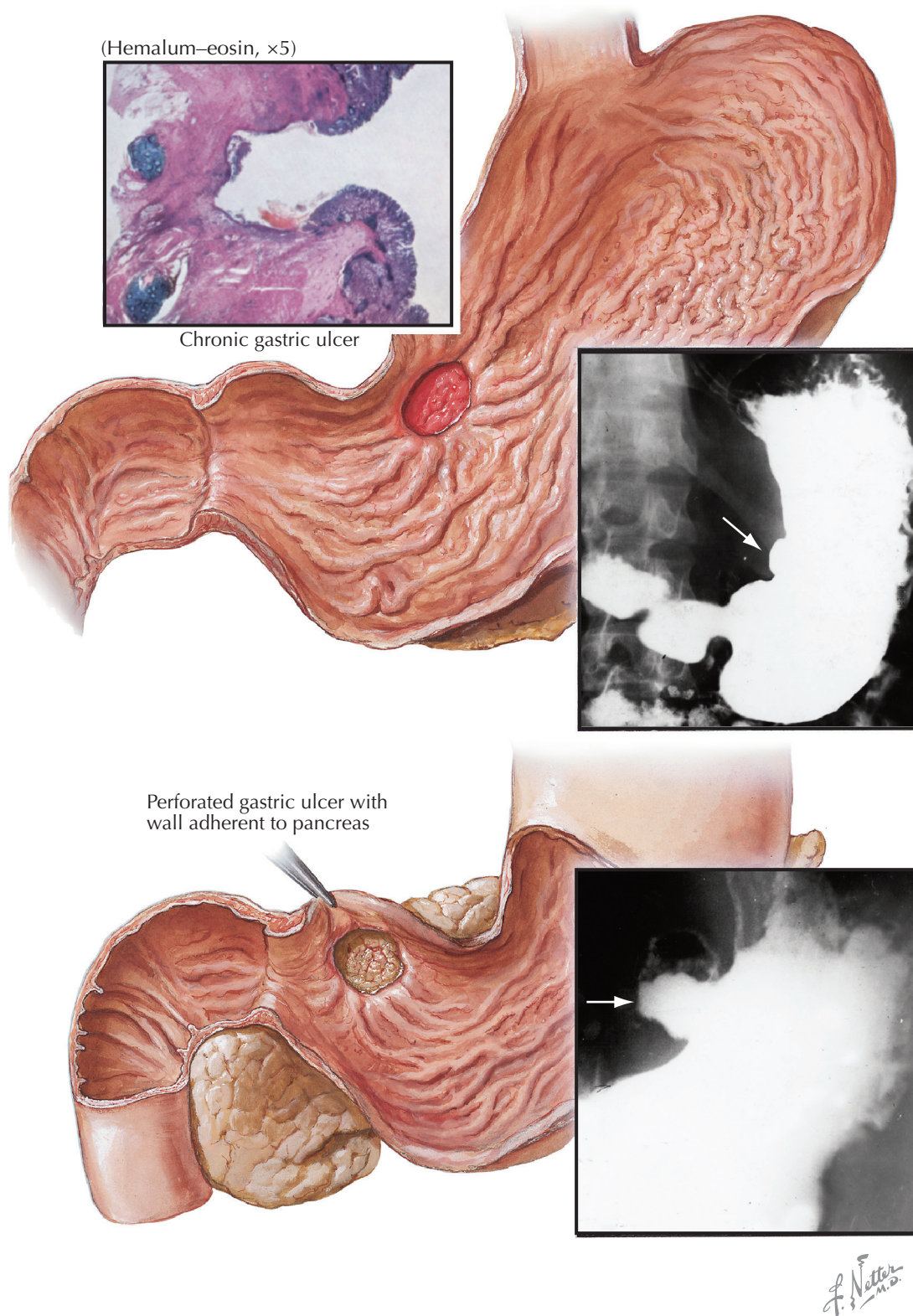
Subacute ulcer
with chronic
changes



Serosal
aspect

patient's history and the shallowness of the ulcer, if identified radiologically, may justify the diagnostic use of this term. The symptoms of subacute ulcer are the same as those of an acute or a chronic ulcer. In addition, a subacute ulcer may run a symptom-free course for an indefinite period of time, and its presence may become evident only after a sudden massive hemorrhage or after the dramatic signs of acute perforation or the less dramatic ones of "chronic perforation."

On the x-ray screen or film, a subacute ulcer is usually demonstrable at or near the *lesser curvature*. The *niche* is, as a rule, clearly outlined and sharply delimited from the contour of the curvature. It is a fixed deformity, remaining stationary during the radiologic study, in contrast to the greater part of the lesser curvature, which participates freely in the peristaltic activity. When the wall of the ulcer is edematous, the apparent depth may be exaggerated.



CHRONIC GASTRIC ULCER

The chronic gastric ulcer is almost invariably single, although scars of previous ulcers that have healed can be found in association with the sole active chronic lesion. Not infrequently, a duodenal ulcer develops simultaneously with a chronic gastric ulcer.

Most benign chronic gastric ulcers occur at or *near the lesser curvature* of the stomach in its midarea and, frequently, on the posterior wall near the lesser curvature. They arise less commonly at the cardiac portion of the stomach or near the pyloric ring. Only rarely does an ulcer on the greater curvature prove to be benign.

Chronic gastric ulcers vary considerably in size, but about 80% of them are less than 1.8 cm in diameter. The ulcer is usually round, but at times it may be elongated. The margins of a chronic ulcer are raised and, usually, considerably undermined, as a result of the retraction of the muscular strata, whose continuity has, in a chronic ulcer, always been interrupted. Fibrotic tissue, covered, at times, by a fibrinous, purulent exudate, forms the floor of the ulcer. The *penetrating* ulcerative process may also involve the serosa, which subsequently becomes thickened by production of fibrotic tissue.

At times, obliterative endarteritis appears in the blood vessels on the floor of the chronic peptic ulcer. The associated veins sometimes show evidence of thickening. Thrombosis of the veins and arteries may occur, sometimes with endarteritis in the same vessel. The nerves at the floor of the ulcer occasionally display perineural fibrosis.

The dominant and also most characteristic symptom of chronic gastric ulcer is epigastric pain, which the patient locates at some place between the xiphoid process and the umbilicus, or somewhat left of this line toward the left costal margin. The intensity and character of the pain, which the patient may describe as “cutting,” “gnawing,” or “burning,” depend upon a variety of factors, such as the location, size, and “activity” of the ulcer and the sensitiveness of the individual patient. The pain may radiate to the back, usually to the level of the 8th to 10th thoracic vertebrae. Rhythmic and periodic recurrence of pain is rather typical, but is by no means absolutely pathognomonic of a chronic ulcer (or sufficiently invariable as to exclude the possibility of a malignant growth). Shortly after ingestion of food, the pain usually disappears, only to recur $\frac{1}{2}$ to 1

hour after the meal. It may abate spontaneously before the next intake of food. This *food-comfort-pain rhythm*, as it has been called, may persist or may respond more or less satisfactorily to medical treatment. It may fade gradually and disappear suddenly, failing to reappear for many months, or even years, if the ulcerating, penetrating, or accompanying inflammatory processes have slowed to a stop. If, on the other hand, the pain becomes more intense, or loses its periodic rhythm and becomes persistent, this should always be taken as an ominous sign of increasing danger of further complications.

Though the patient's history and complaints, as well as a careful physical examination, will be helpful in diagnosing a gastric ulcer, the final diagnosis is generally made endoscopically or by radiologic contrast studies. Radiologically, the chronic gastric ulcer is characterized by a niche projecting from the barium-filled stomach. As a rule, the niche is deeper than that of a subacute ulcer, though it is not always possible to determine the exact depth of the crater from the size of a niche, owing to the variability in the thickness of the edematous and swollen wall.

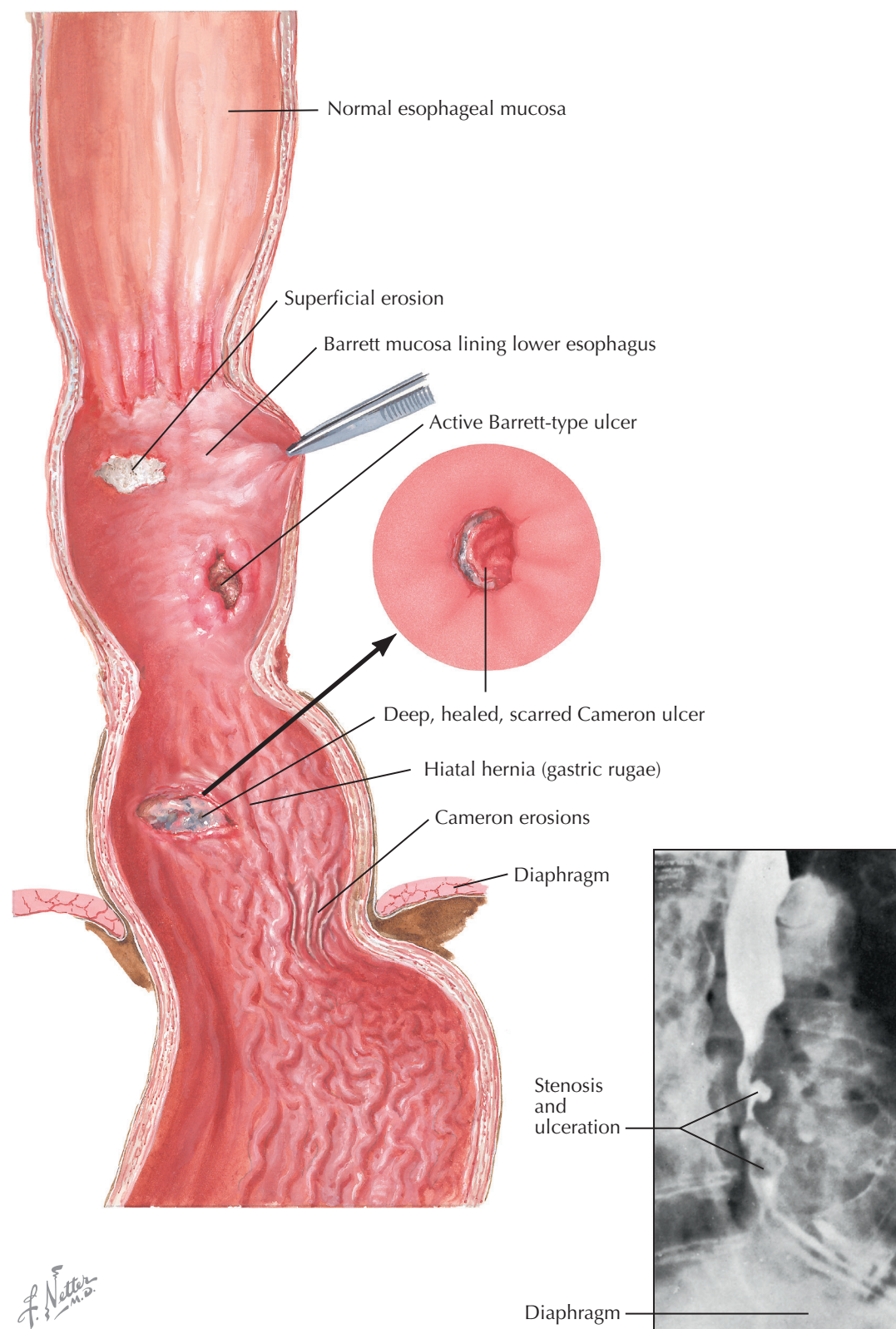
CAMERON LESIONS AND DISORDERS OF THE CARDIA

Cameron lesions are either gastric erosions or linear ulcerations that occur at the level of the diaphragm in patients with a hiatal hernia sac. Cameron lesions were first described in 1986 by Cameron and Higgins, who discovered them in a series of patients. They occur in approximately 5% of patients who undergo upper endoscopy and are found to have a hiatal hernia. They are more common in elderly patients and in those with large sliding hiatal hernias. The cause of these lesions is either mechanical trauma or ischemia secondary to sliding of the hiatal hernia. Medication effects from NSAIDs as well as acid peptic disease also play a part in their formation. Most patients with Cameron lesions present with iron deficiency anemia, although overt upper gastrointestinal bleeding can be seen. Treatment of a Cameron ulcer varies; the use of antisecretory agents should be the first line of therapy. In addition, stopping any caustic medications should be advised. For those patients with persistent symptoms or findings, a surgical procedure should be recommended which mainly focuses on reducing the hiatal hernia and preventing its recurrence.

Ulcers within the stomach are classified based on their location and their association with duodenal ulcers. Ulcers within the cardia are considered type 4 ulcers and have low basal acid output and no relationship to duodenal ulcers. In this respect they are very similar to type 1 ulcers, which are located in the gastric body. Type 2 ulcers located in the antrum and type 3 ulcers located within 3 cm of the pylorus are more likely to have higher basal acid output and to be related to duodenal ulcers. Type 4 cardia ulcers form from abnormally low defensive mechanisms of the stomach as a result of reduced production of bicarbonate or mucus or an increase in prostaglandin secretion. Atrophic gastritis caused by *H. pylori* which migrates proximally from the antrum also plays a role. These factors can increase the mucosal disruption that NSAIDs cause in the stomach.

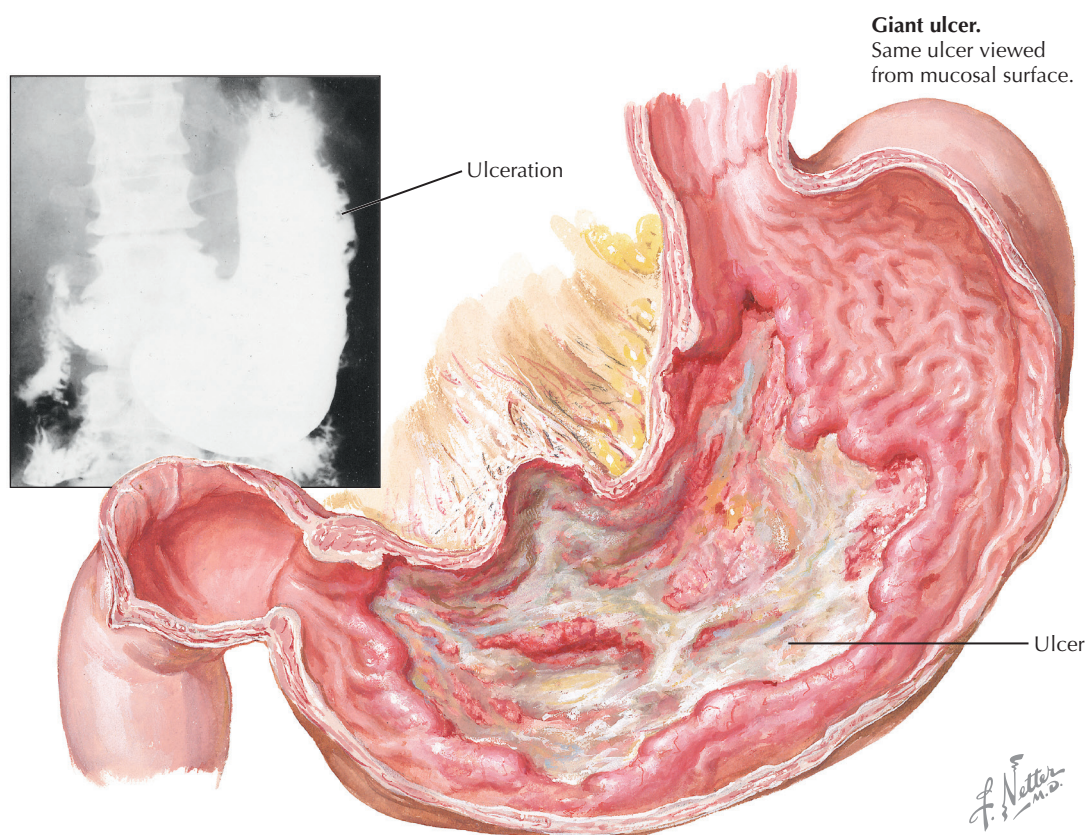
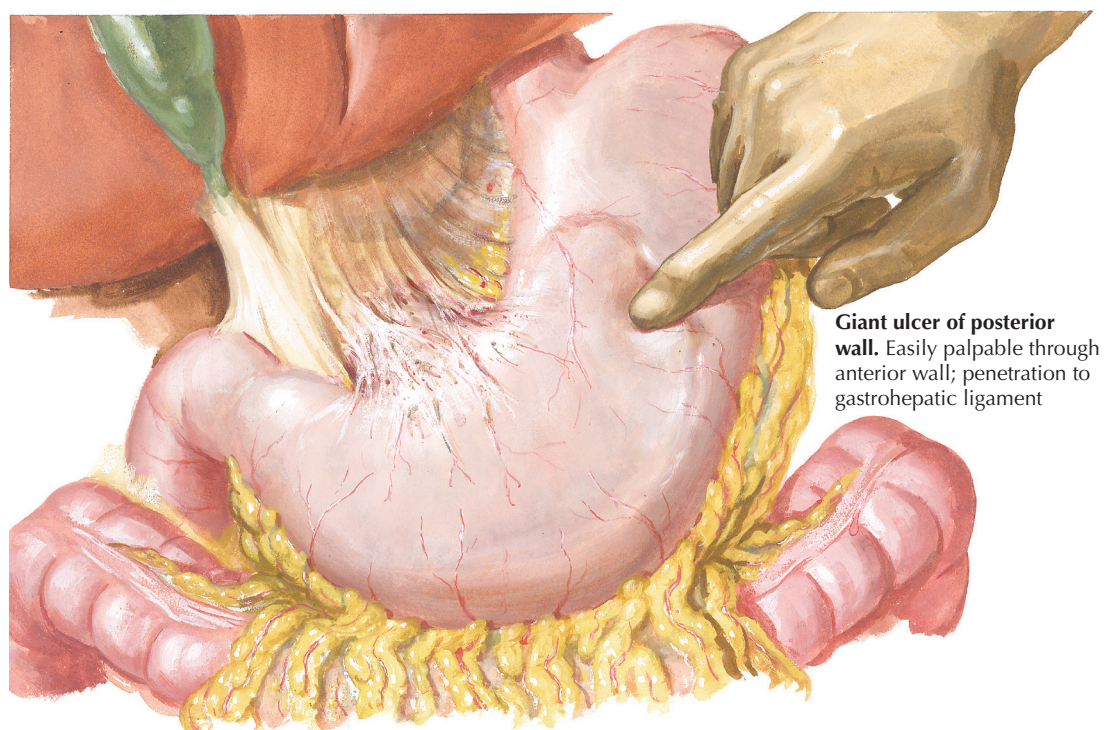
Intestinal metaplasia in the cardia is mainly a result of *H. pylori* infection. In this case, the entire stomach generally is infected with this organism and the pathologic consequences of atrophic gastritis and intestinal metaplasia are seen. In these individuals, the stomach is generally pale or patchy white, with a reduction in gastric folds. Biopsies throughout the stomach typically reveal atrophy, and pH testing often reveals a high pH of 6.0 to 7.0. Histologic examination may not reveal *H. pylori* infection, so it is important to test for the microbe with alternative tests, such as stool antigen or breath tests. This is unlike intestinal metaplasia of the distal esophagus, or *Barrett esophagus*, in which the underlying mechanism is pathologic acidic, nonacidic, or bilious reflux that leads to the change. One distinguishing characteristic is that in true intestinal metaplasia of the distal esophagus, the goblet cells stain with alcian blue, whereas in intestinal metaplasia of the cardia, this is not the case.

The prevalence of cancer of the gastric cardia is increasing, but the prevalence of distal gastric cancers is decreasing. Distinguishing gastric cardia cancers



from distal esophageal cancers can be extremely challenging. The true cardia arises from the gastroesophageal junction with a small 1- to 4-cm extension into the proximal stomach. In some instances, the cardia mucosa extends into the distal 1 to 2 cm of the esophagus, making anatomic distinctions between the cardia and esophagus difficult. Gastric cardia cancers are generally a result of *H. pylori* infection (type A cancers). In these cases, examination of the stomach reveals diffuse atrophy and examination of the esophagus reveals an

absence of Barrett esophagus. In a second subset of cancers, type B cardia cancers, the cause is related to Barrett esophagus, with extension into the cardia. These cancers are often indistinguishable from true distal esophageal cancers, which arise from the gastroesophageal junction; endoscopic examination of the esophagus reveals Barrett esophagus, but examination of the remaining stomach is often macroscopically and microscopically normal. Autoimmune gastritis can also lead to cancer, although it is a rare occurrence.



GIANT GASTRIC ULCER

Giant gastric ulcers are rare in the overall group of gastric ulcers, especially since upper endoscopy evaluation has become available and ulcer treatments with proton pump inhibitors and for *H. pylori* have also become available. The site of origin is usually *on the posterior wall of the gastric body* and may progressively involve the lesser curvature by extension. The ulcers may *penetrate the gastrohepatic ligament* and even involve the liver and pancreas. They are particularly deceptive because the flattened floor of the ulcer is extensive, so that it resembles an atrophic area of gastric mucosa. A very similar pathologic picture can be produced acutely by the corrosive action of acids or alkalis. When caustic agents are involved, however, the contrast material puddles in the prepyloric region and on the posterior wall of the stomach if the patient assumes a supine position immediately after the accident of ingestion.

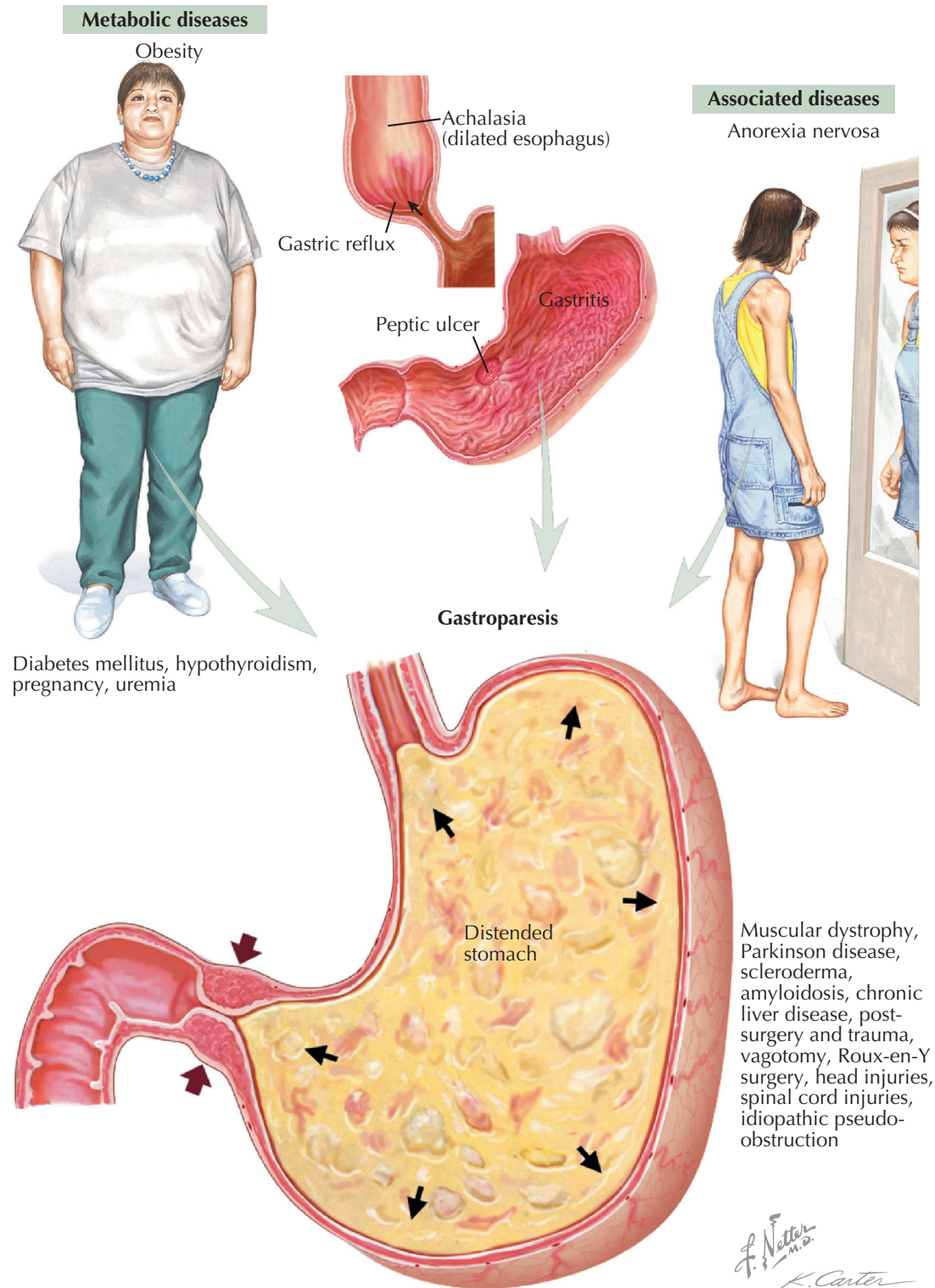
In the past, giant gastric ulcers were usually thought to be carcinomas. They now are considered benign lesions that can be properly treated with vigorous medical management. Upper endoscopy is needed for biopsies to evaluate for carcinoma and to assess for *H. pylori*. Benign ulcers are treated with proton pump inhibitors; healing can take months. Surgical explora-

tion may lead to extensive surgery. Ulcers of this magnitude, and particularly those in the prepyloric region in the absence of a caustic ingestion history, must be considered malignant until proven otherwise by biopsy. Adenomatous changes of serious malignant importance can occur in giant ulcer craters just as they can in the smaller ulcers of the stomach.

Patients with giant benign gastric ulcers are older than patients with smaller ulcers and have more aggressive disease, reflected by a higher incidence of bleeding, anorexia, weight loss, and emergency admis-

sion. Patients usually have a long history of ulcer disease, and usually ulcer symptoms have been present for at least 4 to 6 months. The great majority of these patients are over the age of 50. The patient may have lost much weight and may show advanced stages of malnutrition. Many have fairly far advanced peripheral vascular disease, with involvement of the mesenteric arterioles in an arteriosclerotic process, and, perhaps because of this diminished blood supply, the ulcer has proceeded to its large size. Perforation or massive hemorrhage as a terminal event is not unusual.

ASSOCIATED GASTRIC/ESOPHAGEAL DISEASE



GASTROPARESIS

Gastroparesis is a chronic symptomatic disorder of the stomach characterized by delayed emptying without evidence of mechanical obstruction. The delay in gastric emptying can have a number of causes, including antral hypomotility, pylorospasm, gastric dysthymias, and lack of interstitial cells of Cajal. Symptoms from gastroparesis include nausea, vomiting, early satiety, postprandial fullness, and, in some patients, upper abdominal pain. This classic motility disorder of the stomach can lead to marked dysfunction in patients,

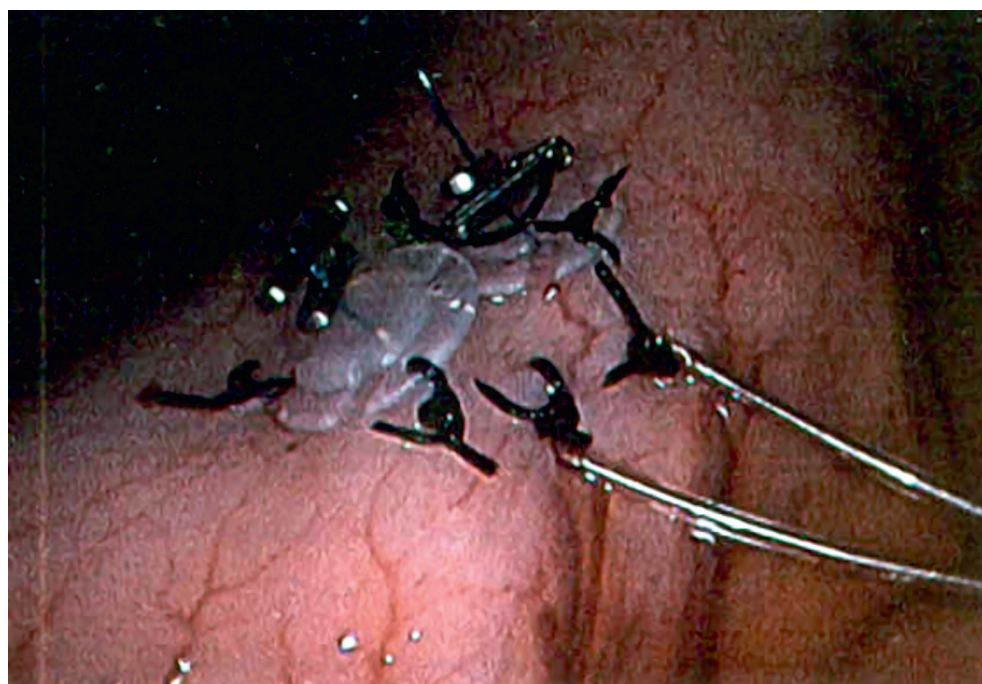
with a poor quality of life. Gastroparesis is identified by recognizing the clinical symptoms and documenting delayed gastric emptying. The three main causes are diabetic, postsurgical, and idiopathic. Management of gastroparesis includes assessing and correcting dehydration and malnutrition, if present; maintaining nutritional intake; relieving symptoms; improving gastric emptying; and, in diabetics, controlling glycemia. The nutritional state should be managed by oral dietary modifications. Medical treatment entails

use of prokinetic and antiemetic therapies. Although in many patients symptoms can be controlled with medical therapy, some patients remain markedly symptomatic, with progressive weight loss. For refractory cases, a jejunostomy feeding tube, gastric electric stimulator, and pyloromyotomy may need to be considered. Unfortunately, current approved treatment options do not adequately address the clinical need. Attention is being given to the development of new effective therapies for symptomatic control.

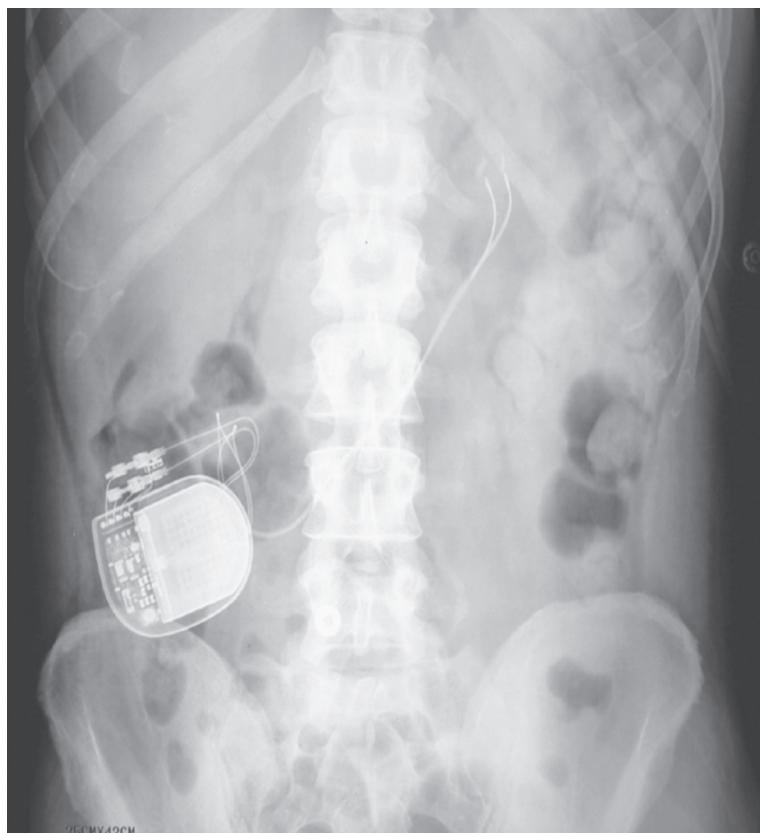
GASTRIC ELECTRICAL STIMULATION FOR GASTROPARESIS

Gastric electrical stimulation is an emerging treatment for refractory gastroparesis. There are several techniques for stimulating the stomach. First, in gastric electrical pacing the goal is to entrain and pace the gastric slow waves with low-frequency, high-energy, long-duration pulses. Pacing at 10% higher than the basal rate is used to try to accelerate gastric emptying and to improve dyspeptic symptoms. Second, stimulation with high-frequency, low-energy, short-duration pulses has been shown to decrease symptoms but has less effect on gastric emptying; it may affect proximal stomach function and activate sensory afferent nerves to reduce symptoms. Third, sequential gastric neurostimulation of the stomach has been used to entrain gastric slow waves.

High-frequency gastric electrical stimulation at 12 cycles per minute has received humanitarian approval by the Food and Drug Administration for treatment of chronic, refractory nausea and vomiting secondary to diabetic or idiopathic gastroparesis. Stimulating wires are placed into the gastric muscle at the greater curvature during laparoscopy or laparotomy. These leads are attached to an electric stimulator (pacemaker), which is placed in a subcutaneous abdominal pouch. An initial study demonstrated effectiveness in 20 of 26 patients, with a decrease in nausea and vomiting at 3 and 6 months; gastric emptying of liquids, but not solids, was improved. In long-term follow-up, 3 of 24 patients underwent total gastrectomy because of unsatisfactory results, and in 3, the stimulator was removed because of erosion or infection. A subsequent study reported on 33 patients with chronic gastroparesis. After implantation, the electrical stimulator was turned on or off in a randomized, double-blind, crossover design. Patients felt better when the stimulator was on, although the decrease in vomiting that occurred was not statistically significant. Long-term follow-up over 1 year showed a decrease in the mean vomiting frequency from 25 to 6 times per week. In addition, there was an improvement in the overall quality-of-life score and a mild improvement in gastric emptying. Complications were infection in 3 patients and electrode penetration of the stomach wall in 1 patient. An open-label study in 25 patients reported an overall improvement from “severe” to



Positioning of the gastric electrodes



Radiograph of the stimulator and electrodes

“moderate” in symptoms of nausea and vomiting of 40%. There was an infection rate of 15%, requiring removal of the stimulator. Recent reports in both diabetic and idiopathic gastroparesis with blinded on and off periods of stimulation did not show significant improvements in symptoms; however, with long-term open-label stimulation over 1 year, a reduction of symptoms was seen.

Carefully designed studies are needed to determine the overall effectiveness of gastric electrical stimulation, which type of patient will likely respond, and the optimal stimulation parameters. Studies suggest that the patients most likely to respond are those with diabetic gastroparesis, those with main symptoms of nausea and vomiting, and those not taking regular narcotic analgesic medications.

FUNCTIONAL DYSPEPSIA

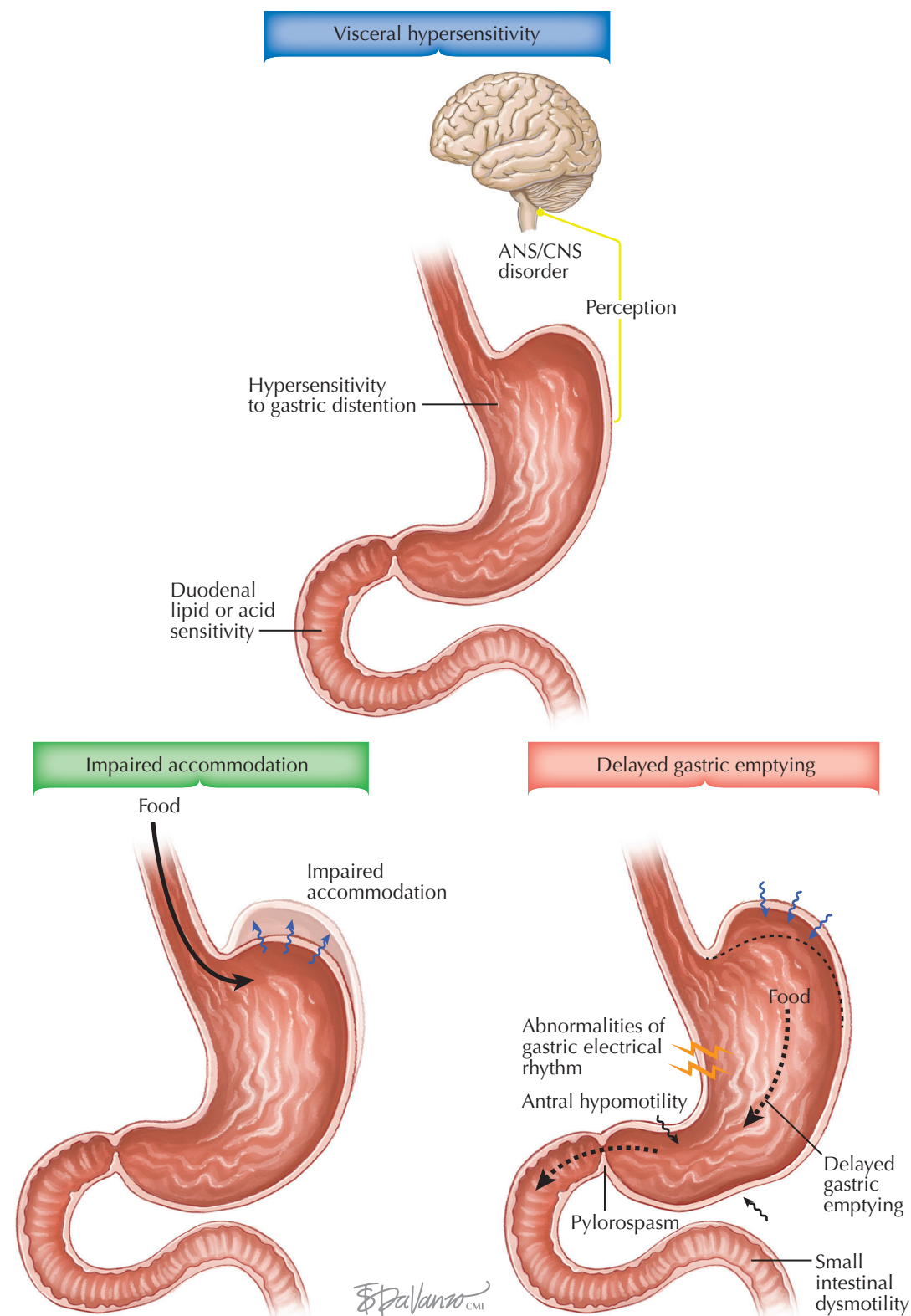
Dyspepsia refers to symptoms originating in the upper gastrointestinal tract; the term is used to describe upper abdominal pain or discomfort, early satiety, and postprandial abdominal bloating or distention. Some examples of structural or biochemical disorders causing dyspepsia include gastroduodenal ulcer, gastritis, GERD, and gastric cancers; medication side effects may also be a cause. In many patients, the cause of dyspepsia is idiopathic and not obvious after an evaluation including the history, a physical examination, blood work, and upper endoscopy; this is termed *functional dyspepsia*. *ROME criteria* for functional dyspepsia developed to help describe these particular patients include the following requirements: (1) the presence of one or more of the following: bothersome postprandial fullness, early satiation, epigastric pain, or epigastric burning; and (2) no evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms. Functional dyspepsia in the *ROME* classification is divided into (1) postprandial distress syndrome characterized primarily by early satiation and postprandial fullness; and (2) epigastric pain syndrome characterized primarily by epigastric pain and burning.

Several mechanisms have been proposed for the pathogenesis of functional dyspepsia. The *gastric acid or inflammation hypothesis* suggests that gastric acid or inflammation from gastric acid, bile, GERD, or *H. pylori* infection is responsible for symptoms. The *motor disorder hypothesis* suggests that gastric motility disorders, such as gastroparesis, impaired fundic accommodation, antral distention, or gastric dysrhythmias, are important. The *visceral hypersensitivity hypothesis* proposes exaggerated symptoms in response to physicochemical stimuli, such as distention, contraction, acid, and bile. The *psychological hypothesis* suggests that some of the symptoms are related to or enhanced with depression, anxiety, or a somatization disorder.

There are several pathophysiologic alterations of gastric motility and sensation in functional dyspepsia. Delayed gastric emptying, impaired gastric accommodation to a meal, and visceral hypersensitivity are important pathophysiologic factors in functional dyspepsia. One or more of these factors may be detected in two thirds of patients with the disorder.

Delayed gastric emptying is present in approximately a third of patients with functional dyspepsia. It has been suggested that the severity of postprandial fullness and vomiting is correlated with delayed gastric emptying, although some studies could not confirm this. Functional dyspepsia patients with delayed gastric emptying may respond better to prokinetic agents than patients with normal emptying. The role of prokinetic agents in improving gastric emptying and symptoms is inconsistent, however.

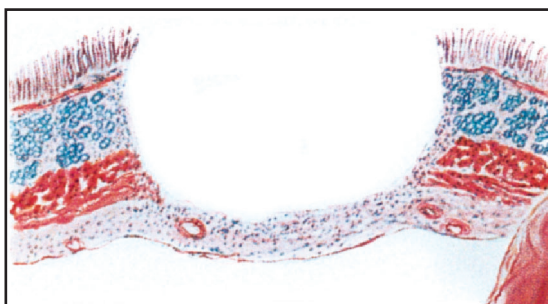
Regional gastric function abnormalities may be present in many dyspeptic patients and appear to correlate with dyspeptic symptoms. Normally, the stomach accommodates to a meal by relaxation of the gastric fundus and corpus, providing the meal with a reservoir and enabling a volume increase without a rise in intragastric pressure. Impaired fundic accommodation has been found in a third of patients with functional dyspepsia. Impaired proximal gastric accommodation was associated with early satiety and subsequent weight loss. In research studies, impaired fundic accommodation can be assessed using a gastric barostat, scintigraphy,



ultrasonography, radionuclide imaging of the gastric wall with single-photon emission computed tomography, or satiety testing with consumption of water or a liquid nutrient drink.

Visceral hypersensitivity or augmentation of visceral afferent sensation (nociception) may be a major cause of symptoms in functional dyspepsia. A third of patients have increased sensation to gastric and small intestinal distention. When the stomach is stimulated by increasing volumes or increasing intragastric pressures, patients experience symptoms at volumes that

physiologically normal subjects do not (*allodynia*), and they have more pain at levels when the physiologically normal subjects begin to have pain (*hyperalgesia*). The symptoms may result from an exaggerated visceral sensory perception of normal physiologic events. Brain activation by visceral stimulation with gastric distention is being studied in functional dyspepsia using positron emission tomography and functional magnetic resonance imaging. Patients with functional dyspepsia may have abnormal activation of the cortical and subcortical sites in response to gastric distention.



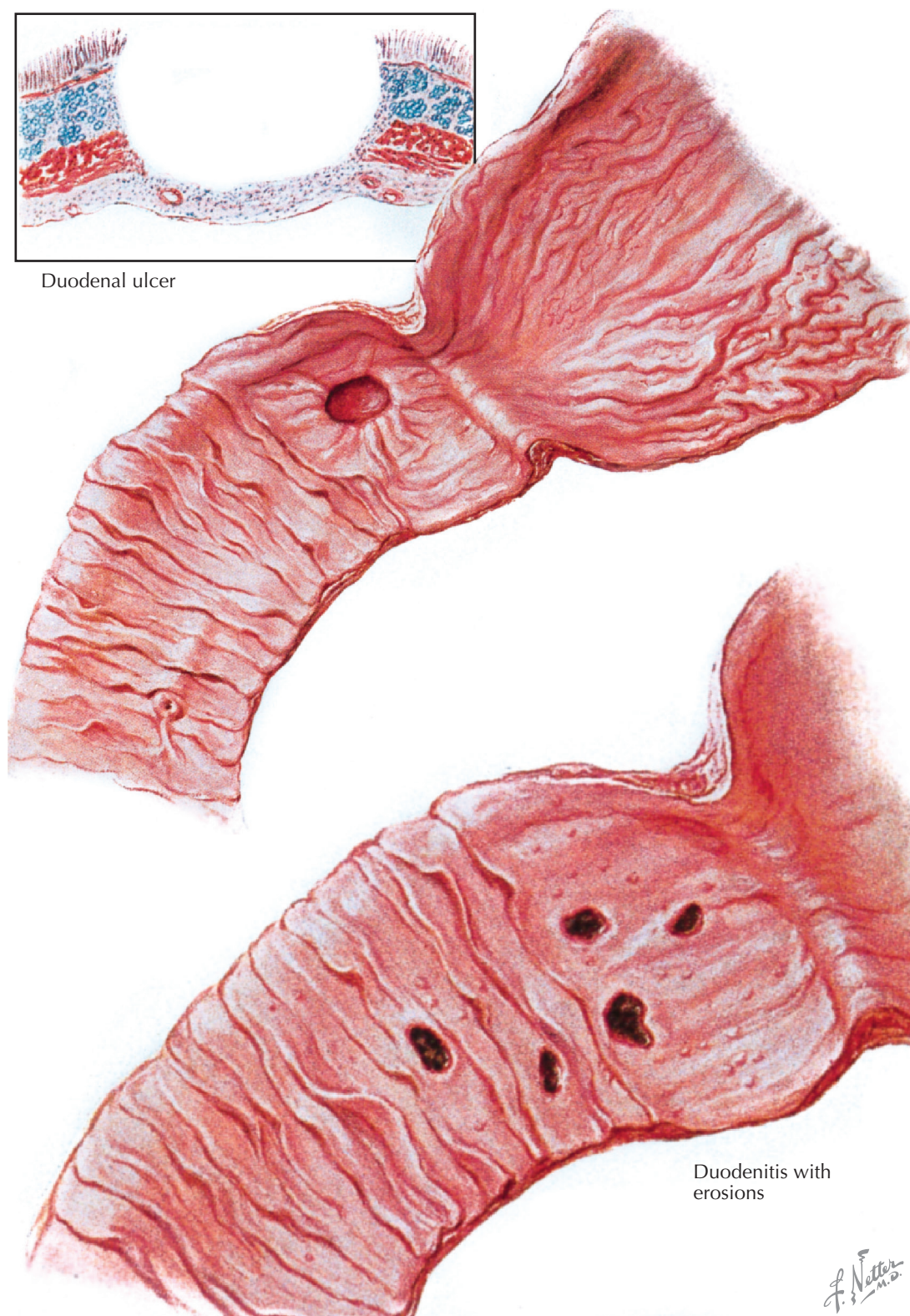
Duodenal ulcer

PEPTIC ULCER: DUODENITIS AND ULCER OF DUODENAL BULB

Duodenitis refers to an inflammation of the mucosa in the duodenal bulbar region. Duodenitis is usually diagnosed endoscopically, often when it is performed for abdominal pain or evidence of acute or chronic gastrointestinal bleeding. The diagnosis may be supported in radiologic contrast studies when the mucosa of the most proximal part of the duodenum appears somewhat mottled and when, fluoroscopically, spasms and an increased motility of the duodenal cap can be observed. The inflamed duodenal mucosa has a relatively strong tendency to bleed, even in the absence of an actual ulcerative process. At times, however, duodenitis may be associated with *multiple superficial erosions*. On the other hand, diffuse duodenitis may also be present in association with a characteristic chronic peptic ulcer. Duodenitis is usually confined to the most proximal parts of the duodenum, but, occasionally, the antral mucosa as well may participate in the inflammatory reaction. Medical treatment for duodenitis is the same as that for peptic ulcer. Massive hemorrhages from duodenitis with erosion may, in rare cases, make exploration necessary, although, as a matter of general principle, surgical intervention is not recommended unless the source of the bleeding has been determined.

More common, and clinically more important, is the *chronic duodenal ulcer*. With rare exceptions, this lesion is seated within the duodenal bulb. It develops with essentially the same frequency on the anterior or posterior wall. The average size of a duodenal ulcer is 0.5 cm, but the ulcers on the posterior wall are usually larger than those on the anterior wall, mainly because the former, walled off by the pancreas lying below the ulcer, can increase in size without free perforation. Causes of these duodenal ulcers include *H. pylori* infection and side effects from NSAIDs.

The duodenal peptic ulcer is usually round and has a punched-out appearance, but as a small ulcer it may sometimes be slitlike, crescent shaped, or triangular. The chronic ulcer, in contrast to an acute ulcer that stops at the submucosa, involves all layers. It penetrates to the muscular coat and at times more deeply. An ulcer on the anterior wall may show a moderate amount of proliferation, whereas that on the posterior wall will give evidence of considerable edema and fibrosis. Healing may proceed just as it does with a gastric ulcer,



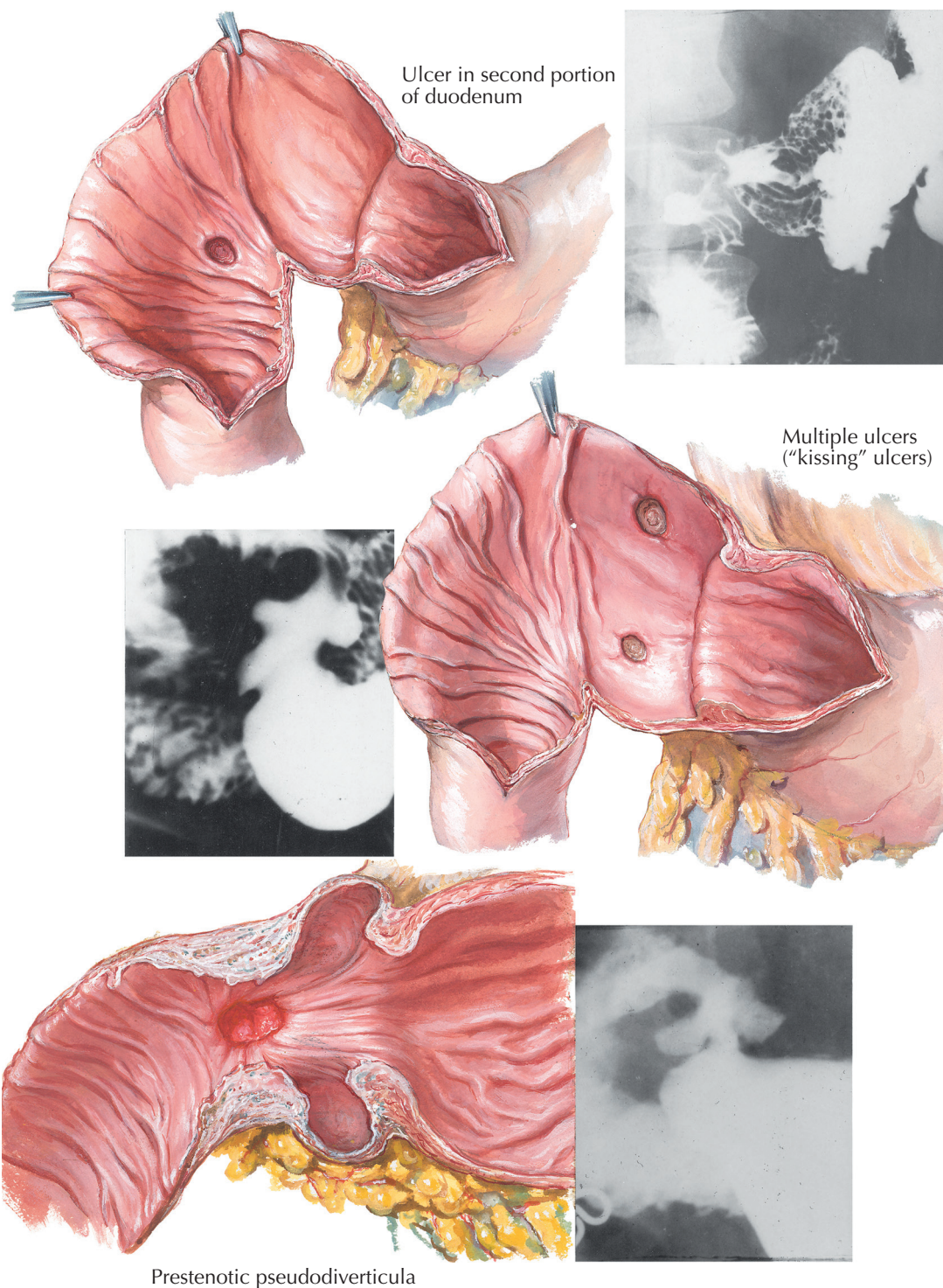
Duodenitis with erosions

with disappearance of the crater and bridging of the gap by formation of fibrous tissue covered by new mucous membrane, but healing becomes more difficult once the destruction of the muscular layer has gone too far.

The symptoms of a chronic duodenal ulcer are, as a rule, typical and are characterized by periodic episodes of gnawing pain, usually located in the epigastrium. The pain occurs 1 to 2 hours after meals and may be relieved by food.

Roentgen examination reveals the classic features of deformity: (1) a niche corresponding to the actual ulcer crater, (2) a shortening of the upper curvature of the bulb, and (3) contraction of the opposite side, which probably is the result of spasms of the circular muscle fibers in the plane of the ulcer or of edema and *cicatrization* (the process of healing to produce scar tissue). Radiating folds due to puckering from scar formation are sometimes demonstrable at the edge of the niche.

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PEPTIC ULCER: DUODENAL ULCERS DISTAL TO DUODENAL BULB; MULTIPLE ULCERS

Peptic ulcers in a region distal to the duodenal bulb are rare, and their frequency, altogether probably less than 5% of all duodenal ulcers, decreases with their distance from the pylorus. *Ulcers in the second portion of the duodenum* give rise to the same symptoms and are beset with the same dangers and complications as are ulcers of the bulb. The acute clinical picture and later significance, however, may be far more complex because of the functional and anatomic implications for the adjoining structures. By the edema of its margin and surroundings, by penetration or by shrinkage, such an ulcer may cause obstruction and eventually stenosis of any one of several structures (the papilla of Vater, the lower part of the common bile duct, and one or both of the pancreatic ducts), so that chronic pancreatitis and/or biliary obstruction with jaundice may result. Deep penetration may give rise to a choledochoduodenal fistula. The presence of duodenal ulcers distal to the duodenal bulb should raise concern for the presence of Zollinger-Ellison syndrome, or gastrinoma, in which excessive gastrin is secreted, leading to excessive secretion of gastric acid.

Multiple chronic ulcers of the duodenum, surprisingly, are not uncommon. Their frequency is 10% to 20%, according to statistical data obtained from cases coming to autopsy. As a rule, the number is restricted to two; only in rare instances have more than two been found. When ulcers develop on both adjacent anterior and posterior walls, they are referred to as "kissing" ulcers. Only a very small percentage of patients with an active duodenal ulcer have also an active gastric ulcer.

A great variety of anatomic changes and roentgenologic deformities of the duodenum can be associated with an ulcer or can develop during the course of its extension or involution. One of the most typical duodenal deformities occurring with the ulcerative process is the *prestenotic pseudodiverticulum*. Seen from the

lumen, it represents a relatively flat, sinuslike indentation, located usually between the pylorus and the site of the ulcer or proximal to a duodenal stricture resulting from a cicatricial (scarring) remnant of an ulcer. Although all layers of the duodenal wall participate in the formation of such a pouch, the situation differs from that of a true duodenal diverticulum, in that the mucosa has not evaginated through a small muscular gap. The pseudodiverticula need not cause any clinical symptoms, but they produce quite characteristic radiographic

pictures, which have been described as a "typical bulbus deformity" in cases of chronic peptic ulcer, though, at times, their differentiation from an active duodenal ulcer niche may be difficult. Although the prestenotic diverticulum is usually single, the development of multiple pouches is not rare. Often two pseudodiverticula may appear symmetrically in the upper and lower parts of the duodenal bulb, and a third one may deform the bulb into what has been called roentgenographically the "cloverleaf bulbus."

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COMPLICATIONS OF GASTRIC AND DUODENAL ULCERS

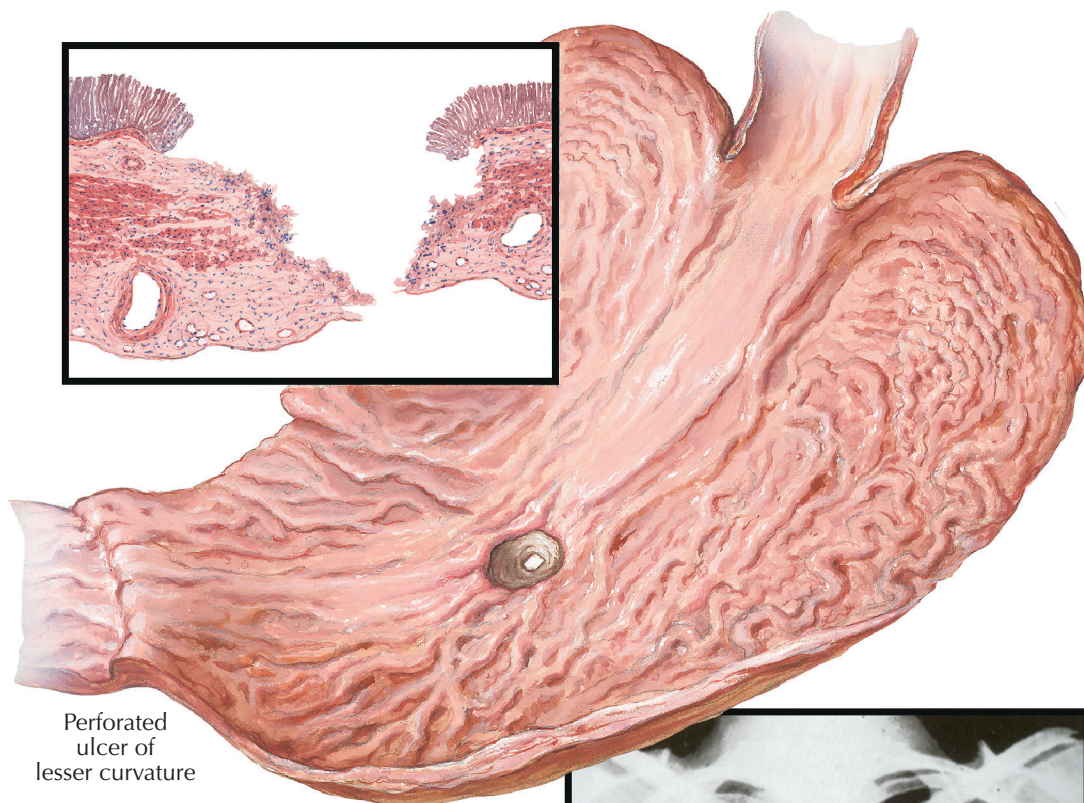
GASTRIC PERFORATION

The two most serious complications of gastric or duodenal peptic ulcers are perforation and hemorrhage. The frequency of acute perforations in patients hospitalized for peptic ulcer varies from 2% to 25%. Perforation occurs with far greater frequency in men than in women. It is also recognized that peptic ulcer tends to perforate more often in individuals between the ages of 25 and 50 years than in younger or older persons. Fortunately, these two complications appear to have decreased over the last several decades with the widespread use of flexible upper endoscopy for diagnosis of ulcer disease and the advent of improved medical treatments with proton pump inhibitors and for *H. pylori* infection.

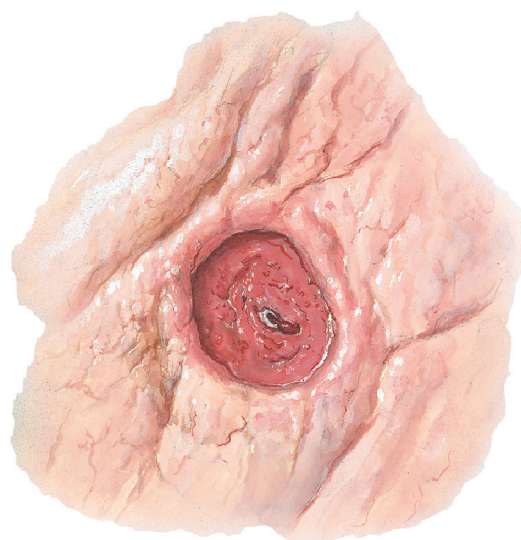
The previous duration of an ulcer, of either the stomach or the duodenum, seems to have no influence on the speed with which the ulcerative and inflammatory processes penetrate the muscular coat and the serous layer. An acute peptic ulcer may rapidly penetrate or perforate the gastric or intestinal wall, so that, in some instances, the patient may fail to give any history of typical ulcer symptoms. Many chronic ulcers, on the other hand, may exist for years without progressing so far in depth as to implicate the serosa, although no chronic ulcers with severe and persistent symptoms or recurrent or calloused ulcers are ever exempt from the potential danger of a perforation. The rapidity with which the digestive effect of the strongly acid gastric juice destroys the layers of the wall and approaches the serosa cannot be anticipated.

Once perforation has taken place, the location of the ulcer plays an important role as to the clinical presentation of the patient. *Ulcers of the anterior wall* of both the stomach and the duodenum have a greater access to the "free" peritoneal cavity than do those on the posterior wall. From the posterior aspects, the ulcer may proceed to penetrate the underlying organs such as the left lobe of the liver, the pancreas, or the gastrohepatic ligament. These may block the ulcer and prevent the entry of gastric or duodenal contents into the peritoneal cavity. This "walled-off" perforation, in which a new floor for the ulcer has been organized outside the visceral wall, has been called *chronic perforation* or *penetration*; the term *subacute perforation* has been reserved for certain tiny ruptures in the serosa, which occur only with a relatively slowly advancing penetration of a chronic gastric ulcer. In such instances, fibrinous adhesions to contiguous parenchymal organs or peritoneal attachments have come into existence, as a result of periinflammatory tissue reactions, long before the ulcer has penetrated to the serosal layer. The adhesions intercept the small amount of gastric content that might escape through what are usually very small apertures, thus enveloping the fluid, which may lead to the development of localized abscesses.

A *free perforation* occurs most frequently with ulcers of the anterior wall of the duodenal bulb. The hole resulting from an acute perforation is usually round, varying in diameter from 2 to 4 mm. One of the characteristic features of these holes is their sharp edges,



Perforated ulcer of lesser curvature



Bleeding gastric ulcer



Air under right diaphragm resulting from perforated ulcer

which make them appear to have been punched out. The surrounding tissue may fail to show any signs of chronic induration, edema, or inflammation.

The clinical picture of an acute and free perforation, whether it occurs in the stomach or in the duodenum, is often dramatic. At the moment of perforation, the patient is seized by a sudden, excruciating, explosive pain, which is of a severity "almost beyond description." It is felt all over the abdomen and may radiate to the chest and shoulder. The patient is pale, the haggard face

is covered with cold perspiration, and the suffering is expressed in every feature of the countenance. In an effort to reduce the abdominal pain, the patient flexes the thighs toward the abdomen, which is extremely rigid and tender ("doubling up"). During this early phase, which may last from 10 minutes to a few hours, in part depending on the amount and type of gastrointestinal content released into the peritoneal cavity, the body temperature is subnormal; the pulse and blood pressure remain within the normal range (or the rate of

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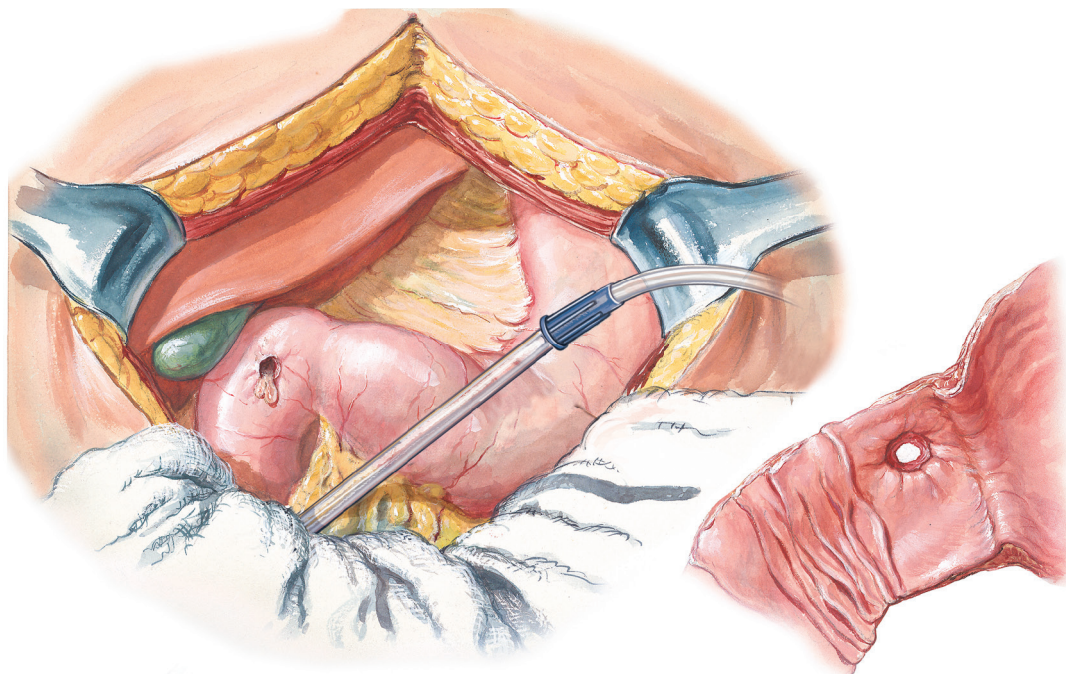
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the pulse may even be rather slow), though respiration may assume a superficial and panting character. Within a short time, in some instances introduced by a period of apparent subjective improvement, all the typical signs (e.g., nausea, vomiting, dry tongue, rapid pulse, fever, leukocytosis) of a severe, acute, diffuse peritonitis appear. The tenderness, in the early phase confined mostly to the upper part of the abdomen, has spread, as a rule, over the total abdominal area. It may be excessive in the lower right quadrant if, with a perforation of a duodenal ulcer, the intestinal material is dissipated in the right lumbar gutter along the ascending colon.

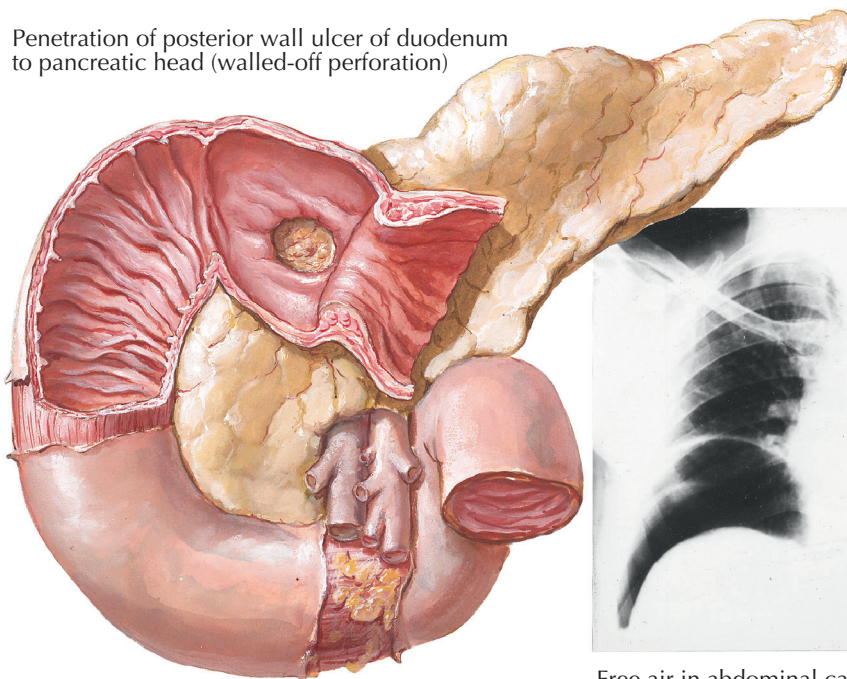
The differential diagnosis between a perforated gastric or duodenal ulcer and pancreatitis or a mesenteric thrombosis may be rather difficult in some cases, but such difficulties are seldom encountered with a ruptured appendix. Other conditions, such as an ectopic pregnancy, ruptured diverticulum, renal colic, acute episodes of biliary tract diseases, acute intestinal obstruction or volvulus, and, in some instances, coronary thrombosis, must also be considered.

The sign that is most helpful in confirming the suspected diagnosis of ulcer perforation is the *presence of free air* in the peritoneal cavity, particularly in the *subphrenic space*, demonstrable by upright x-ray examination. If it is possible for the patient to sit or stand, the air will accumulate under the diaphragm. Escaped air is present, in rare cases, under the left diaphragm only; not infrequently air may be detected under both diaphragmatic leaves and, more usually, under the right leaf only.

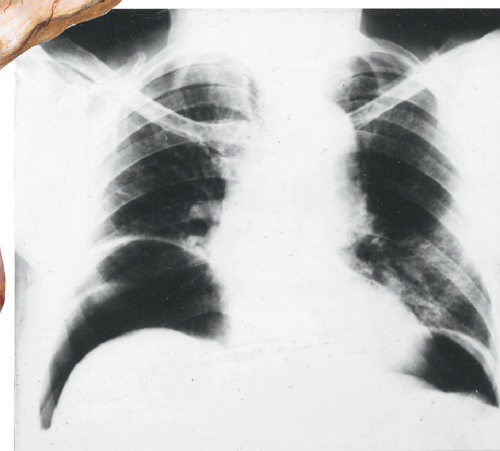
Surgical intervention is nearly always required in the form of exploratory laparotomy and closure of perforation with peritoneal wash. Conservative treatment, including intravenous fluids, antibiotics, nasogastric aspiration, and bowel rest, is occasionally used with consultation with surgery, if the patient is nontoxic and clinically stable. With the finding of air, operation is usually indicated without delay. The prognosis of a perforated gastric or duodenal ulcer is better the earlier an operation is performed. The mortality rate increases when the operation is performed more than 6 hours after perforation. The operation of choice is often a subtotal gastric resection in younger individuals who are in good general condition. This is true if the surgeon is permitted to work within the first 6 hours after the ulcer has perforated, under optimal hospital conditions, with carefully supervised anesthesia, with the support necessary to combat successfully the vascular collapse and infection. When the patient is in poor general condition, efforts to treat conservatively with suction through an indwelling catheter in the stomach, massive antibiotics, and supportive therapy entail a greater risk and are less successful than is surgical treatment, although in some isolated instances the life of the patient so treated has been saved. The simple closure of the perforation, postponing the more definitive surgery, if necessary, until such time as the patient may be in a more favorable condition, should be reserved for cases that come to the surgeon's attention later than 6 hours after the onset of the acute illness, or for elderly patients (over 60 years of age), when the shock tends to



Acute perforation of duodenal ulcer of anterior wall



Penetration of posterior wall ulcer of duodenum to pancreatic head (walled-off perforation)



Free air in abdominal cavity (subphrenic space) following rupture of duodenal or gastric ulcer

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F. Dallanese CM

be massive, or when the cardiopulmonary situation requires an operation of the shortest possible duration. In approximately 60% of cases in which the perforation is closed by simple suture, the more radical operation becomes inevitable at a later time.

The symptoms of a spontaneously closing ulcer perforation (so-called *subacute perforation*) lack the dramatic accents of an "acute" or free perforation. The majority of these patients may not feel more than some intensification of their usual ulcer pains. It happens, not

infrequently, that a perforation is not detected preoperatively in the assessment of a bleeding or intractable ulcer but becomes evident only at surgery or with examination of the pathologic specimen. In other instances the patient, as well as the physician, may have been well aware of the acute event, but the signs pointing to a perforation (e.g., sharp epigastric pain, abdominal rigidity, elevated temperature and pulse rate) disappeared within such a short period of time that operation was deferred as not critical. Sooner or later, however,

COMPLICATIONS OF GASTRIC AND DUODENAL ULCERS

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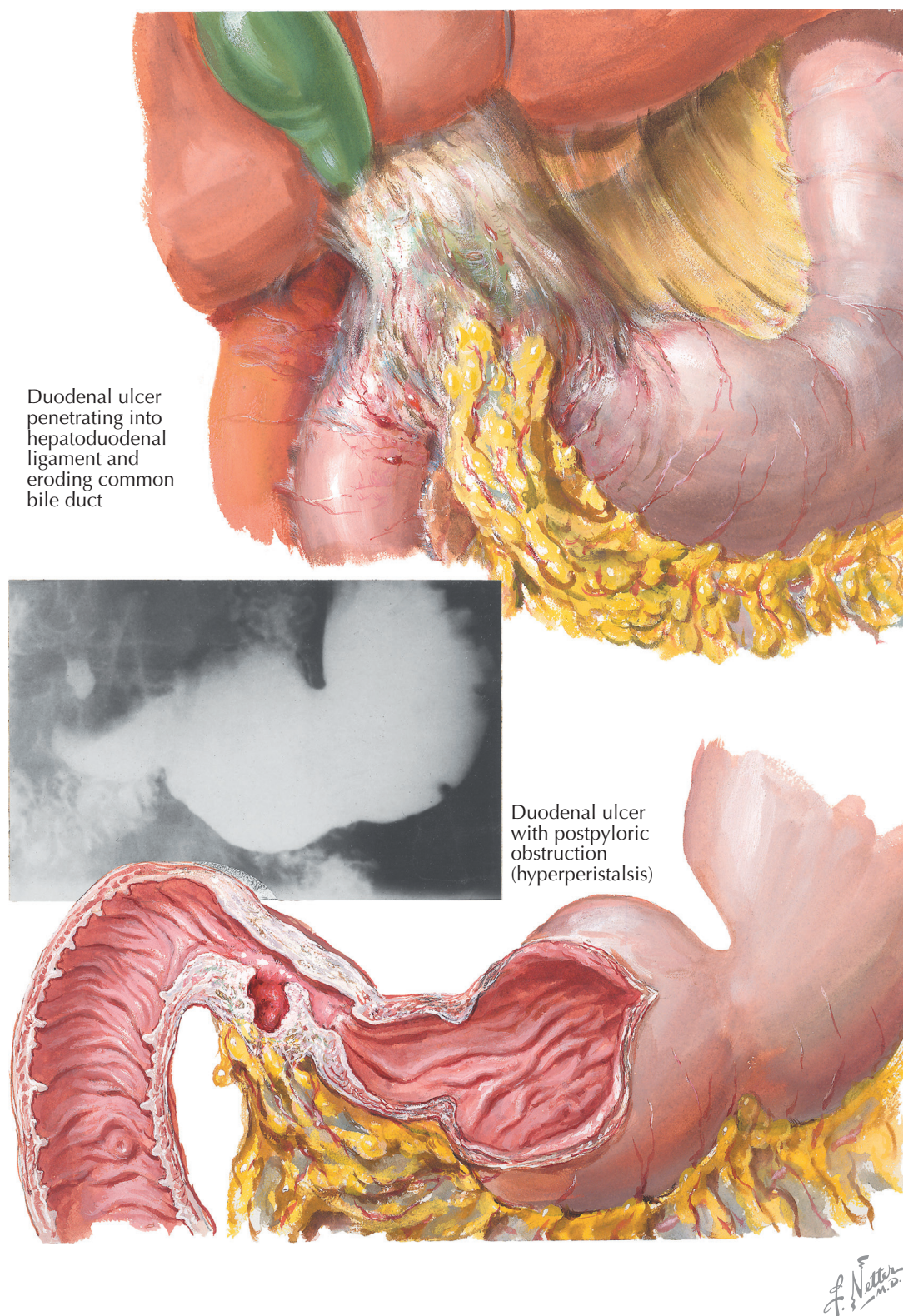
most of these patients must be operated upon because of a localized peritonitis, an abscess that may form in the subphrenic or subhepatic regions, or, later, a partial gastric or duodenal obstruction caused by the massive scar formation.

The erosion of the serosal layer by a chronic peptic ulcer on the posterior walls of the stomach and duodenum and its penetration into a contiguous organ is such a slow process that the actual perforation is rarely detected by the patient. The typical ulcer pains and their relation to and relief as a result of food intake gradually give way to continuous, gnawing, boring pain, which no longer responds to the ingestion of food. The pain may radiate to the back, shoulder, clavicular areas, or umbilicus, or downward to the lumbar vertebrae and the pubic or inguinal regions. Considering the peripheral distribution of pain pathways and their origin in a spinal segment, the site where the patient allocates the radiating pain or the detection of a hyperesthesia in a certain region of the skin may give a clue to determining the organ involved. A classic example of a *chronic perforation* is the *ulcer of the posterior wall of the duodenal bulb*, penetrating into and walled off by the pancreas. In operating for this condition and attempting to remove the entire ulcer with its floor in the pancreatic tissue, one runs the risk of producing a pancreatic lesion that may open accessory pancreatic ducts. It is, therefore, advisable in these cases to leave the ulcer floor untouched after careful dissection of the ulcer from the duodenal wall.

Ulcers located in the upper parts of the *posterior duodenal wall* have a great tendency to *penetrate the hepatoduodenal ligament*. This process is usually accompanied by the development of extensive, fibrous, and thickened adhesions, to which the greater omentum may contribute. The supraduodenal and retroduodenal portions of the common bile duct, taking its course within the leaves of the ligament, may become compromised in these adhesions. As a result of a constriction or distortion of the common duct, a mild obstructive icterus may confuse the clinical picture. Fortunately, perforation into the duct, with a subsequent cholangitis, is a rare event. In the surgical approach to an ulcer of that kind, the anatomic relations of the common bile duct must be kept acutely in mind, whether or not signs of duct involvement are present. Disastrous lesions can be avoided by a preliminary exposure of the duct and by the introduction of a T tube, which serves as a good guide in disentangling the adhesions and exposing the duodenal wall and the ulcer. Very seldom does an acute perforated ulcer of the posterior gastric wall release chyme into the bursa omentalis, producing only signs of localized peritonitis without free air in the abdominal cavity.

PYLORIC STENOSIS

Another complication of the chronic relapsing duodenal, pyloric, or prepyloric ulcer is *stenosis of the pylorus*, which develops gradually as the result of the little-by-little thickening of the duodenal wall and the progressive fibrotic narrowing of the lumen. The incidence of complete pyloric stenosis as a sequel to an ulcer has decreased in recent decades, apparently because of



improved medical management of this type of ulcer and prompt recognition of its initial phases. Medical management involves the use of proton pump inhibitor therapy; treatment of *H. pylori* infection, if present; and, if needed, endoscopic pyloric dilation. When the pyloric lumen begins to narrow, the stomach tries to overcome the impediment by increased peristalsis, and its muscular wall becomes hypertrophic. This is the stage that has been called *compensated pyloric stenosis* because, with these adaptation phenomena, the stomach

succeeds in expelling its contents with only mild degrees of gastric retention. Later, when the lumen is appreciably narrowed, the expulsive efforts of the stomach fail, and the clinical picture will be dominated by incessant vomiting and by distress, owing to a progressive dilatation of the stomach, which, at times, may become massive. This condition of *decompensated pyloric stenosis*, which results in the retention of ingested material and the products of gastric secretion, is, as a rule, irreversible and is an unequivocal indication for surgical

COMPLICATIONS OF GASTRIC AND DUODENAL ULCERS

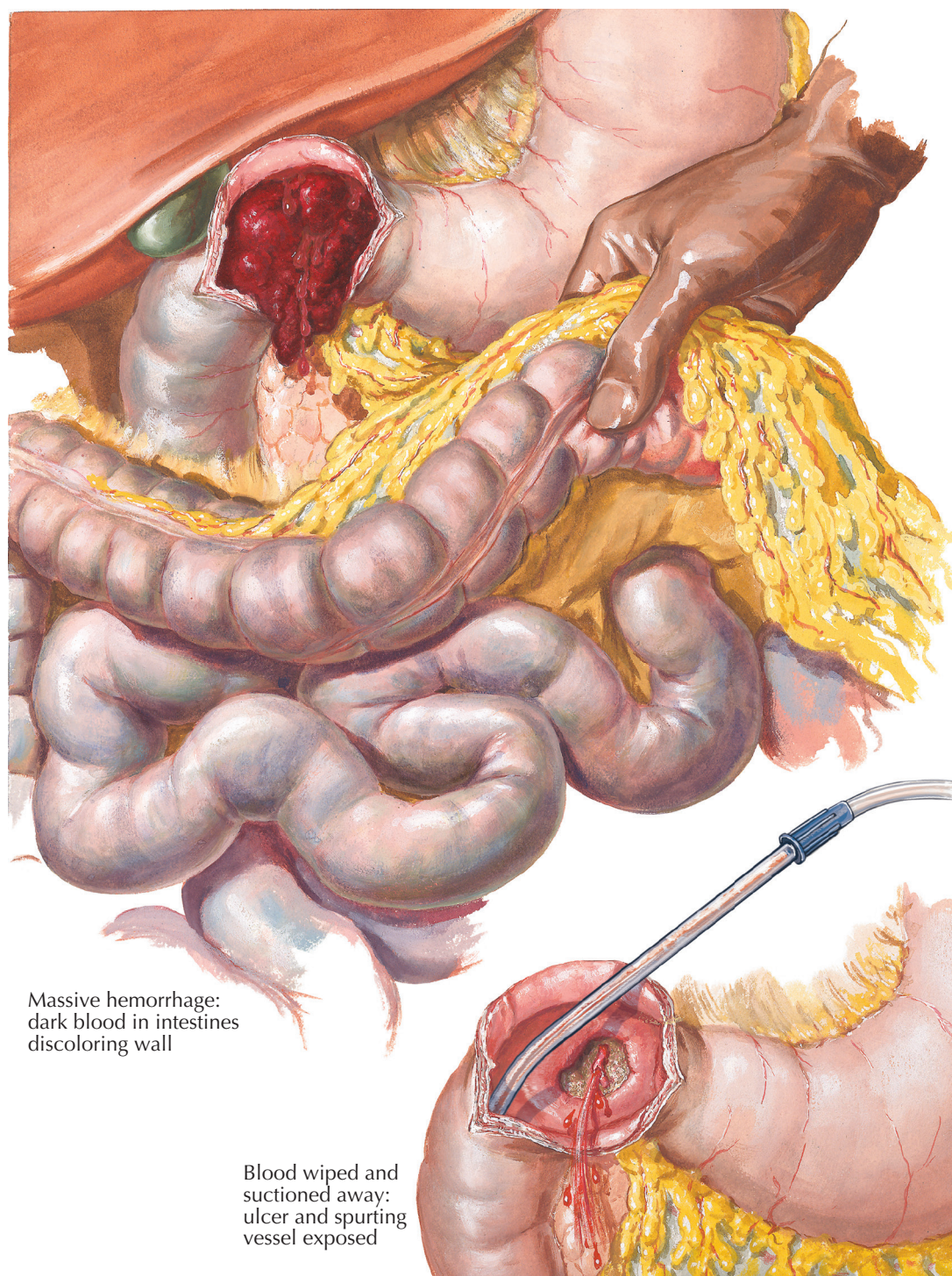
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intervention. The operation of choice is a subtotal gastrectomy, but, in view of the characteristically poor general condition of the patient, the surgeon may sometimes have to resort to less radical procedures, such as a gastrojejunostomy. In the presence of a still-active ulcer, those operations which reroute the gastric content around the duodenum in the simplest fashion should be supplemented by a bilateral vagotomy.

GASTROINTESTINAL HEMORRHAGE

Minor bleeding occurs in the majority of patients with acute or chronic peptic ulcer. "Occult" blood can be found with fair regularity in the stools or gastric juice of most ulcer patients. This is the result of the oozing characteristic of ulcerative lesions. Massive hemorrhage, which, together with perforation, typifies the most dangerous of all ulcer complications, is fortunately far less frequent. Reliable figures of its incidence are not available, but it has been estimated that, of all massive hemorrhages of the gastrointestinal tract, 60% to 75% stem from a peptic ulcer. Obliterative endarteritis or thrombosis of the mucosal and submucosal vessels in the ulcerated tissue may be a natural protection against bleeding from the more superficial ulcers. As a rule, the hemorrhage is caused by erosion into a large vessel, though excessive bleeding occasionally also derives from smaller arteries or veins whose drainage is impaired. A decisive factor for the degree of bleeding is the location of the ulcer. Gastric ulcers have often caused excessive blood loss, but the most frequent origin of a massive hemorrhage is the ulcer of the posterior portion of the duodenal bulb, because here the ulcer can penetrate into the walls of the gastroduodenal and retroduodenal (posterior and superior pancreaticoduodenal) arteries, which course just behind the first portion of the duodenum.

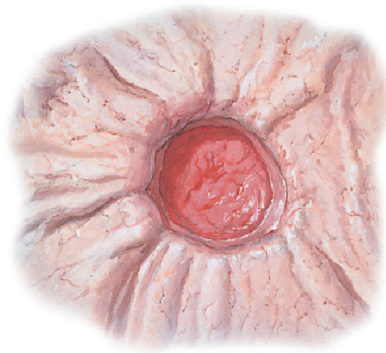
The essential clinical signs of a duodenal ulcer perforated into an artery are massive melena and acute vascular collapse. The shock may appear suddenly and very shortly after the opening of an artery, or it may be delayed for several hours. In striking contrast to the hemorrhages due to gastric ulcer and esophageal ulcers or varices, hematemesis is rare with bleeding from a duodenal ulcer, because the blood, originating from beyond the spastic pylorus, is propelled into the small intestine and does not regurgitate to the stomach. In some cases sudden bleeding comes as a complete surprise to patients who have had no previous complaints or signs pointing to the presence of an ulcer, and this may be the first event to indicate the existence of a "silent" ulcer. The differential diagnosis of the origin of the bleeding and its localization may, at times, be extremely difficult. Emergent upper endoscopy in patients with upper gastrointestinal bleeding is usually indicated. X-ray examination is often of little help, because such a bleeding ulcer may fail to show the usually typical perifocal changes, and because the niche may be filled with blood coagulum. Endoscopic therapy with electrocautery, clipping, or injections is attempted to stop the bleeding, along with giving intravenous fluids and/or blood and with proton pump inhibitor therapy.



Massive and continuous bleeding from an ulcer which cannot be stopped endoscopically should be treated surgically. Repeated hemorrhages are adequate indication for surgical intervention. A rapid major blood loss, the advanced age of a patient, and the presence of shock not immediately responsive to appropriate measures make operation imperative.

Even during operation, it may often be difficult to establish the origin of hemorrhage if it has not been determined before surgery by upper endoscopy.

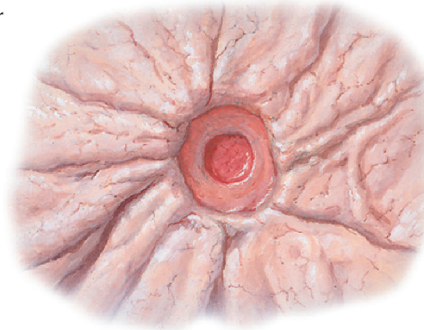
However, endoscopic localization can also be difficult if the bleeding is massive. A bluish discoloration of the upper jejunal loops permits no more than a suspicion that the bleeding has originated in the gastroduodenal or esophageal area. The ulcer itself cannot always be palpated, and only after duodenotomy may the ulcer crater be found. The bleeding can then be provisionally secured by ligation of the bleeding vessel. The final arrest of the hemorrhage, however, may require subtotal resection.



Large gastric ulcer



Healed with puckering



Diminution of size with progressive epithelization

HEALING OF GASTRIC ULCER

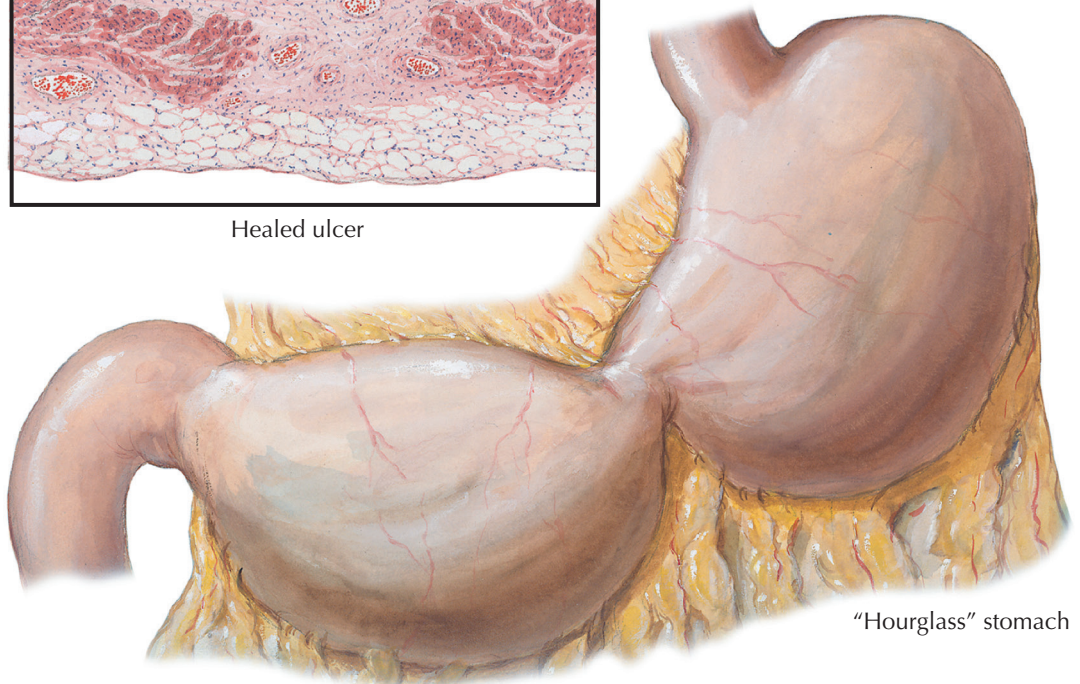
In most cases, gastric ulcers heal without complications. Inflammation and edema of the ulcer wall subside. As a result, the wall tends to become flattened. The fibrinopurulent exudate on the floor of the ulcer separates off, is discarded, and is replaced by healthy granulation tissue and, subsequently, fibrous tissue. The size and depth of the ulcer are reduced, chiefly by cicatrization (a process of wound healing that produces scar tissue) and the contraction of the fibroblasts on the floor and in the wall of the lesion. In addition, the epithelium grows inward from each margin to cover the area of ulceration. From this epithelial layer, projections downward eventually develop, forming simple glands. Finally, the entire area is covered by epithelium. As the contraction of the fibrous tissue progresses, a permanent scar and, in some cases, *radiation of the mucosal folds* develop.

During the healing process the ends of the muscular coat may fuse with the muscularis mucosae. But, although severed ends of the muscular layer approximate one another as a result of the cicatrizing process, restitution of a muscular breach is never complete. This remains as permanent evidence of the original lesion. *Puckering* and radiating streaks on the serosal surface are further evidence of the scar produced in the healing process of the chronic gastric ulcer. This can be seen endoscopically, as medical practice suggests following these ulcers until healing occurs. The healing of a chronic gastric ulcer sometimes is complete, but not infrequently such ulcers are prone to recur, particularly if the newly formed mucous membrane is thin and its vascular supply deficient. In other cases the recurrence of ulcer symptoms is due to an entirely new ulcer, the scar of the original lesion remaining permanent.

The *gradual transition* that occurs in the healing process of a chronic gastric ulcer is demonstrable endoscopically and/or roentgenographically by following the changes in the size of the niche corresponding to the crater of the ulcer. As a result of the healing process, the niche diminishes until it has completely disappeared. At other times, with clinical recurrence of symptoms, the ulcer becomes reactivated and the niche reappears.



Healed ulcer



"Hourglass" stomach

As a result of the healing of a large gastric ulcer, a number of deformities may develop, of which the bilocular or *hourglass stomach* is the best known. It is a rare phenomenon occurring more frequently in women than men, in spite of the higher incidence of gastric ulcer in men. With an hourglass stomach, the viscus is divided into two cavities connected by a channel with a lumen of varying size. The deformity originates mostly from a large ulcer, located in the corpus of the stomach, which has healed by an extensive contracting scar

formation. It rarely causes complete obstruction, but the clinical symptoms are so unspecific, particularly when the original ulcer is still active, that the diagnosis must depend on the results of the x-ray examination. Radiographic evaluation may not yield unequivocal answers, because constriction due to a malignant growth, temporary spasms associated with an active gastric ulcer, and the rare gastric manifestations of syphilis may simulate the x-ray appearance of an hourglass stomach caused by ulcer healing.

GASTRIC POLYPS

BENIGN TUMORS OF THE STOMACH

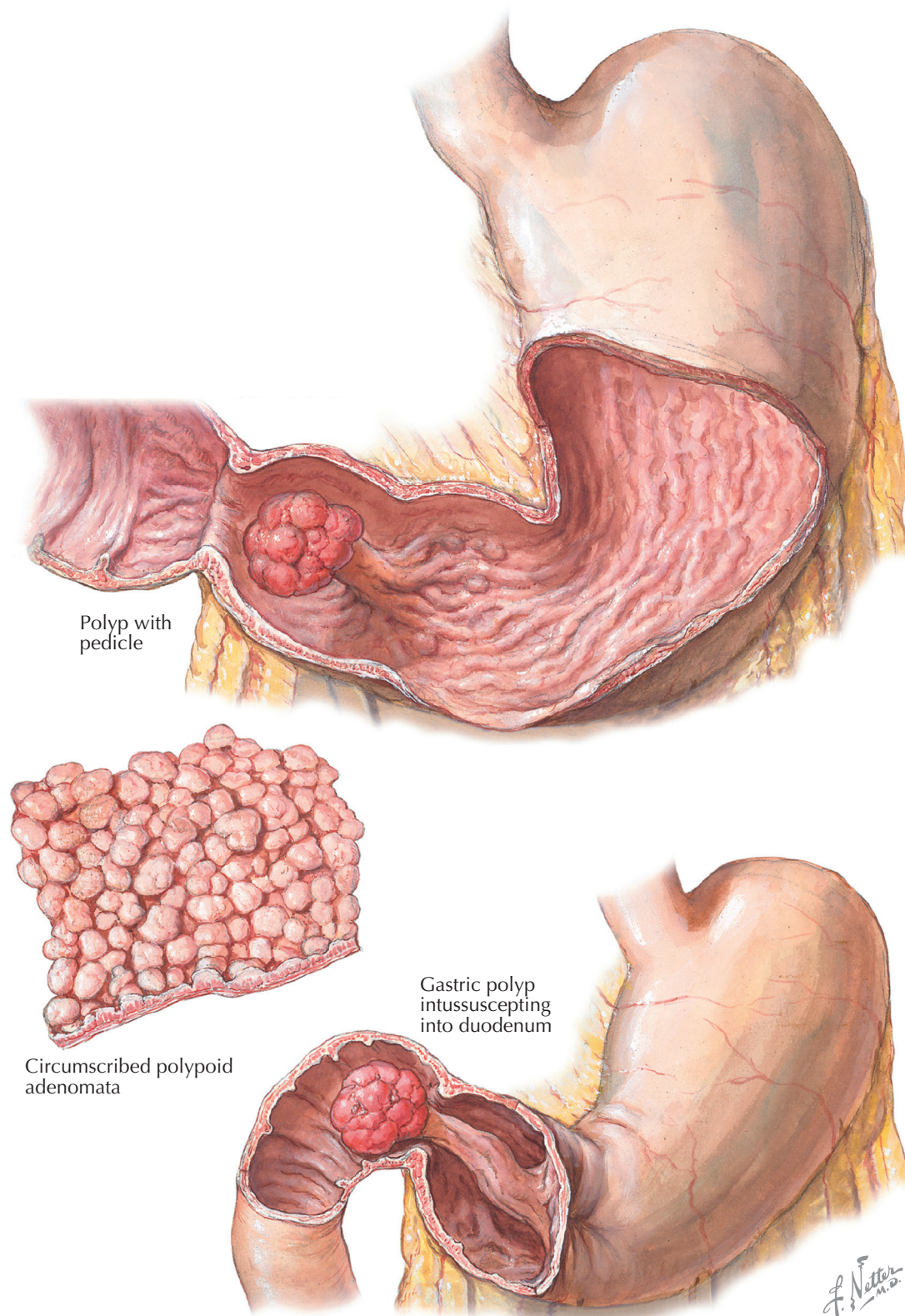
Benign tumors, compared with carcinomas, are relatively rare. They are small and typically do not cause symptoms. With the increasing use of endoscopy and radiologic imaging, small tumors are now more frequently detected incidentally.

Benign tumors are classified as epithelial, submucosal, or ectopic, based on the tissue layer of origin. Epithelial tumors include hyperplastic, fundic gland, and adenomatous polyps. Submucosal tumors include gastrointestinal stromal tumors (GISTs), leiomyomas, lipomas, fibromas, hamartomas, neurofibromas, hemangiomas, eosinophilic granulomas, and inflammatory polyps. Ectopic tissue of the pancreas, called a pancreatic rest, or Brunner gland hyperplasia can lead to benign tumors in the stomach.

Benign tumors are rarely symptomatic. They are most commonly detected when an endoscopic or radiologic examination is performed for another indication. If a benign tumor does enlarge and is located near the pylorus, it may cause symptoms of obstruction. These tumors can chronically bleed, leading to a clinical picture of anemia or acute upper gastrointestinal bleeding. These tumors rarely produce epigastric pain. In such cases, upper endoscopy is needed to distinguish a benign tumor from peptic ulcer disease.

If a tumor is first identified on radiography, barium contrast, computed tomography scanning, or magnetic resonance imaging, the next best diagnostic test is upper endoscopy with biopsy. Biopsy can help with making a histologic diagnosis. Upper endoscopy can also be therapeutic, with complete removal of the benign tumor. The tumor will often require further evaluation with endoscopic ultrasound (EUS). EUS identifies the depth of the lesion and the tissue layer of origin, which is most useful for confirming a diagnosis of subepithelial tumors.

The most important clinical significance of benign tumors is their malignant potential. For this reason, endoscopy with either biopsy or complete resection is necessary. Fundic gland polyps, which arise from the epithelial layer, have become more common with the widespread use of proton pump inhibitors. They only carry malignant potential if familial adenomatous polyposis syndrome is present. Once the histologic diagnosis of fundic gland polyp is confirmed after upper endoscopy with biopsy, and the syndrome is not present, no further therapy or surveillance is needed. Hyperplastic polyps are also epithelial, but in contrast, do have an increased risk of developing into gastric cancer, espe-



cially if they are larger. The recommendation is that all polyps be at least biopsied, and larger ones should be completely resected.

The gastric adenoma, sessile or pedunculated, contains more or less regular epithelial tubules embedded in loose connective tissue. The pedicle of such a solitary "polyp" of the stomach usually is broad where it attaches to the gastric wall, but the stalk is thin and permits free mobility of the tumor. If the tumor is in front of the

pylorus or is pushed in front of it by peristalsis, intermittent partial obstruction may result. The pendulous, to-and-fro movements can give rise to irritation and stretching of the tumor's mucosa, which can lead to epigastric pain and bleeding. In some cases, recurrent or profuse hematemesis may be the first clinical manifestation.

Adenomatous polyps tend to be larger than fundic or hyperplastic polyps and may develop into gastric cancer.

BENIGN TUMORS OF STOMACH

BENIGN TUMORS OF THE STOMACH (Continued)

Once the diagnosis of gastric adenoma is made, the polyp should be completely endoscopically resected. A technique called endoscopic mucosal resection may be required to ensure that the entire adenoma is removed. This requires injecting saline into the mucosa to lift the lesion. After the polyp has been completely removed, the patient will require follow-up endoscopy to confirm that the adenoma has not recurred.

Numerous polyps throughout the gastrointestinal tract are seen in familial polyposis syndromes. These are usually fundic gland polyps but can also be adenomas, both of which may develop into gastric adenocarcinomas. These patients therefore require routine surveillance with upper endoscopy. Hamartomatous polyps or hamartomas are seen in Peutz-Jeghers syndrome and in juvenile polyposis. These polyps, found in the stomach and small bowel, do carry a small risk of malignant transformation, and these patients therefore also require routine surveillance with upper endoscopy.

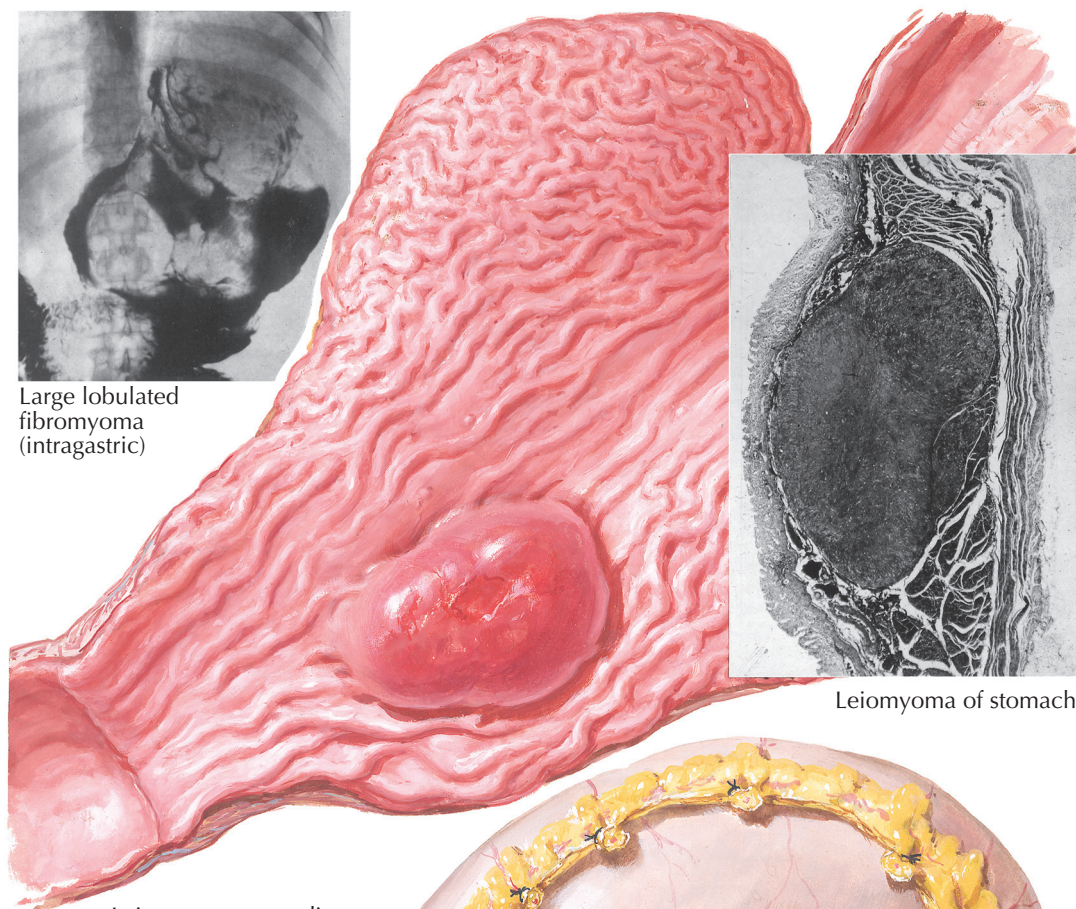
GISTs are the most common type of mesenchymal stromal gastric tumors and arise from the smooth layer. They are typically slow growing, presenting in the fifth or sixth decade of life with abdominal pain or bleeding. Their malignant potential is based on their size and the mitotic index, the latter of which can only be determined after resection. EUS helps to confirm whether the lesion arises from the subepithelial layer, and fine-needle aspiration can provide a histologic diagnosis. EUS will also identify the depth of involvement and any lymph node involvement. Cytology samples show spindle cells, and immunohistochemistry can confirm the diagnosis. A smaller confirmed GIST should be closely monitored with repeat EUS, whereas larger GISTs and those causing symptoms such as pain or bleeding should be completely removed.

Lipomas are common benign tumors that can be seen in the stomach as well as other parts of the gastrointestinal tract. They are slow-growing tumors that are usually incidentally found on upper endoscopy. Depending on their size and location in the stomach, they can cause abdominal pain, bleeding, obstruction, or intussusception. On endoscopy, they appear as smooth, yellow, subepithelial lesions that are soft when gently probed with a closed biopsy forceps (*pillow sign*). Histology shows deposits of adipose tissue in the wall of the gastrointestinal tract. They do not have malignant potential, and there are no current recommendations for resecting all lipomas.

The *leiomyoma* belongs to the group of smooth muscle tissue tumors which include such mixed tumors as fibromyoma, adenomyoma, and others. Histologically, the gastric leiomyoma possesses the same characteristics as myoma does elsewhere in the body. It is usually well encapsulated and grayish-white on the cut surface; it originates from the muscular layers and develops below or within the submucosa. In extremely rare cases such a leiomyoma may enlarge through the serosa to form an extragastric tumor. Intra-gastric tumors may attain such size as to occupy a large part of the lumen. In such instances, they may cause obstruction, or at least serious impairment, of the filling and emptying of the stomach. Smaller tumors, occasionally multiple, usually have no clinical significance. The mucosa above a large leiomyoma is stretched tightly



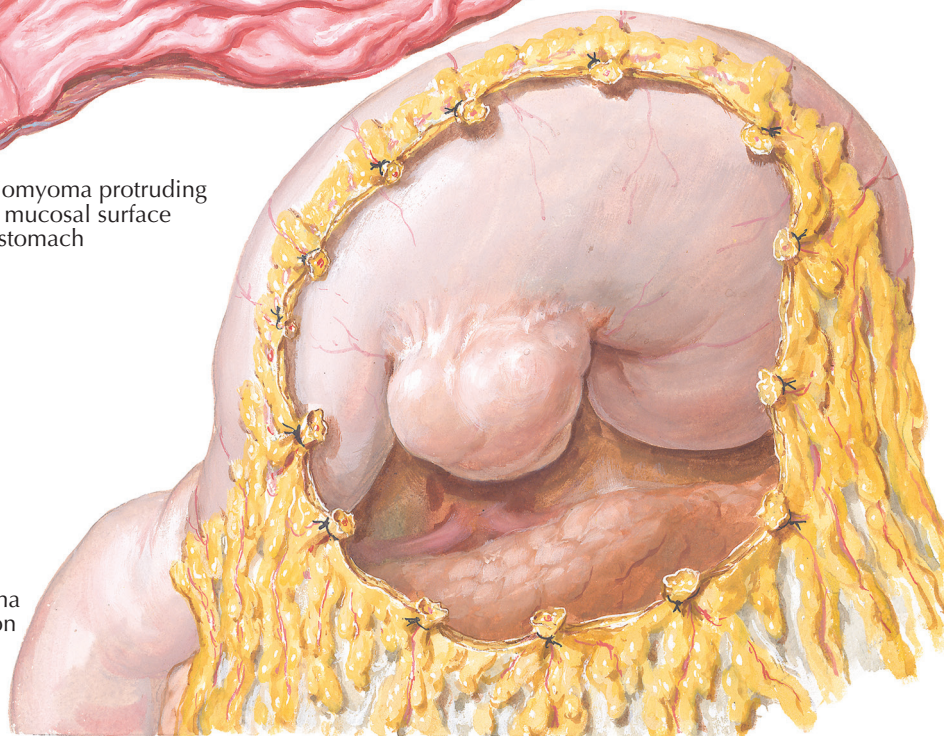
Large lobulated fibromyoma (intra-gastric)



Leiomyoma of stomach

Leiomyoma protruding on mucosal surface of stomach

Neurofibroma protruding on posterior serosal surface of stomach



and tends to ulcerate and, subsequently, to bleed profusely. In addition, the tumors may, rarely, undergo degeneration.

Neurofibroma is a slow-growing neoplasm, usually originating from a nerve sheath coursing along the lesser curvature. The tumor may also occasionally represent part of a generalized neurofibromatosis (*neurofibromatosis type I* or *von Recklinghausen disease*). A neurofibroma may expand in the direction of the lumen and may produce there a submucosal protrusion, or it

may project outward into the peritoneal cavity, in which case it may sometimes become pedunculated. Provided the mucosa is sufficiently stretched, intra-gastric neurofibroma may also give rise to bleeding, as do other benign tumors. If not, they display few, if any, clinical symptoms. Cystic degeneration of a neurofibroma has been reported.

Another rare benign tumor of the stomach is a *hemangioma* (not illustrated). Its specific characteristic is the marked tendency to cause bleeding.

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NEAR CARDIA AND IN FUNDUS

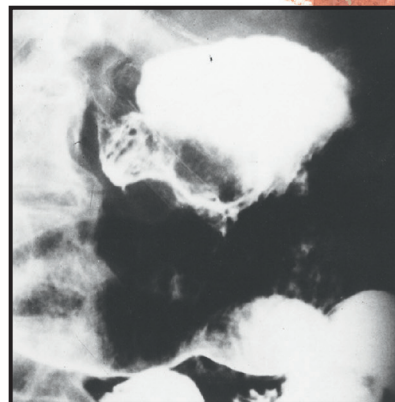
CARCINOMA OF STOMACH

Gastric cancer affects more than 22,000 Americans yearly. Cancer of the stomach is seen more than twice as often in men as in women. It is essentially a disease of middle and old age, about 85% of cases arising after the age of 40. Gastric cancer was previously the most common malignant neoplasm causing death in the male population, but today its incidence has slowly decreased, to between 16% and 25%. The increased incidences of lung carcinoma and esophageal cancer, primarily esophageal adenocarcinoma, have now caused these cancers to become the leading malignant causes of death in men. In women, cancers of the uterus and of the breast are more frequent than of the stomach.

The most common type of gastric cancer is adenocarcinoma, which arises from the glands in the stomach lining. Other kinds of gastric cancer are lymphomas, GISTs, and carcinoid tumors.

Gastric cancer is a multifactorial disease and has several potential contributory factors. *H. pylori* infection is a risk factor in 70% of gastric cancers worldwide, but only 2% of people with the infection develop stomach cancer. The mechanism by which *H. pylori* induces stomach cancer potentially involves the action of *H. pylori* virulence factors such as CagA and chronic inflammation. Smoking increases the risk of developing gastric cancer; in smokers most tumors occur in the upper part of the stomach near the esophagus. Some studies show increased risk with alcohol consumption. Dietary factors are not proven causes, although nitrates and nitrites in cured meats can be converted into compounds that have been found to cause stomach cancer in animals. People may possess certain risk factors, such as those that are physical or genetic, that can alter their susceptibility for gastric cancer. Heredity may well play a part, because not too infrequently gastric cancer has been observed for several generations in members of the same family. A genetic risk factor for gastric cancer is a defect of the *CDH1* gene known as *hereditary diffuse gastric cancer*. Atrophic gastritis, though by no means invariably leading to cancer, is considered by many a precancerous, or at least a potentially precancerous, lesion. Transitional changes from an atrophic mucosa to hyperplastic and papillomatous areas have been demonstrated. Chronic gastric ulcers can rarely undergo malignant transformation. About 17% of all gastric cancers arise in ulcers, and approximately 10% of benign nonhealing ulcers may later become malignant. It is always a matter of primary concern for the physician to exclude malignancy of a gastric ulcer with endoscopic evaluation and biopsies, with follow-up to ensure complete healing of benign gastric ulcers.

The treatment of stomach cancer generally involves a team approach, with surgical, medical, and radiation oncologists. Surgical resection with an adequate lymphadenectomy is essential for a cure. Team members treat patients with chemotherapy and radiation therapy before or following surgery; this has recently been proven to improve the cure rate for this disease. Some patients may undergo only chemotherapy before and after surgery.



Carcinoma of cardia

Carcinoma of fundus

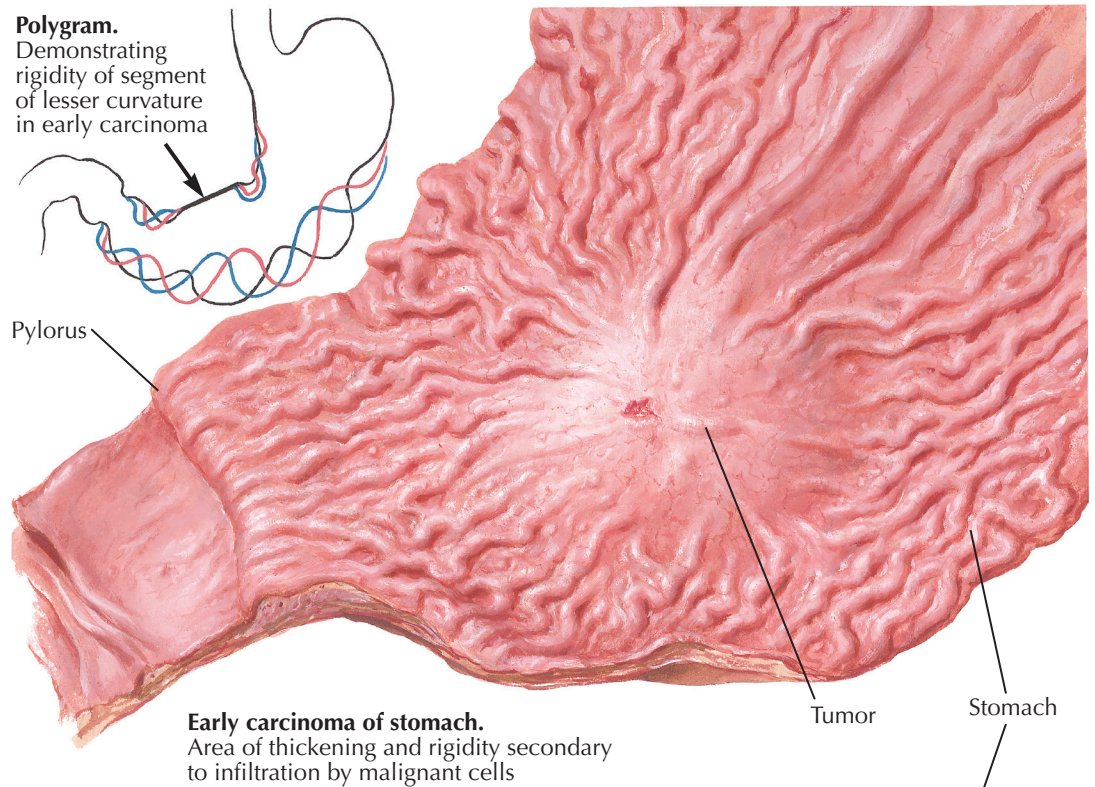
CARCINOMA NEAR THE CARDIA AND IN THE FUNDUS

Gastric cancer may develop in any part of the stomach. From a clinical point of view, by reason of the diagnostic, prognostic, and operative-technical aspects, it is reasonable to differentiate two types of carcinoma in the upper portions of the stomach, namely, those located in the cardia (which involves the gastroesophageal junction) and those occupying the fundus.

The *cardiac carcinoma*, even in its earlier stages, interferes with the free passage of food, causing marked dysphagia. This fact often permits a relatively early diagnosis. Thus, it is not surprising that the operative treatment of these tumors yields probably the best long-term results of treatment of all carcinomas of the stomach. In contrast, *fundic carcinoma*, like other neoplasms in the so-called "silent" gastric zones, remains undiscovered usually for a long time. It often infiltrates

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EARLY CARCINOMA



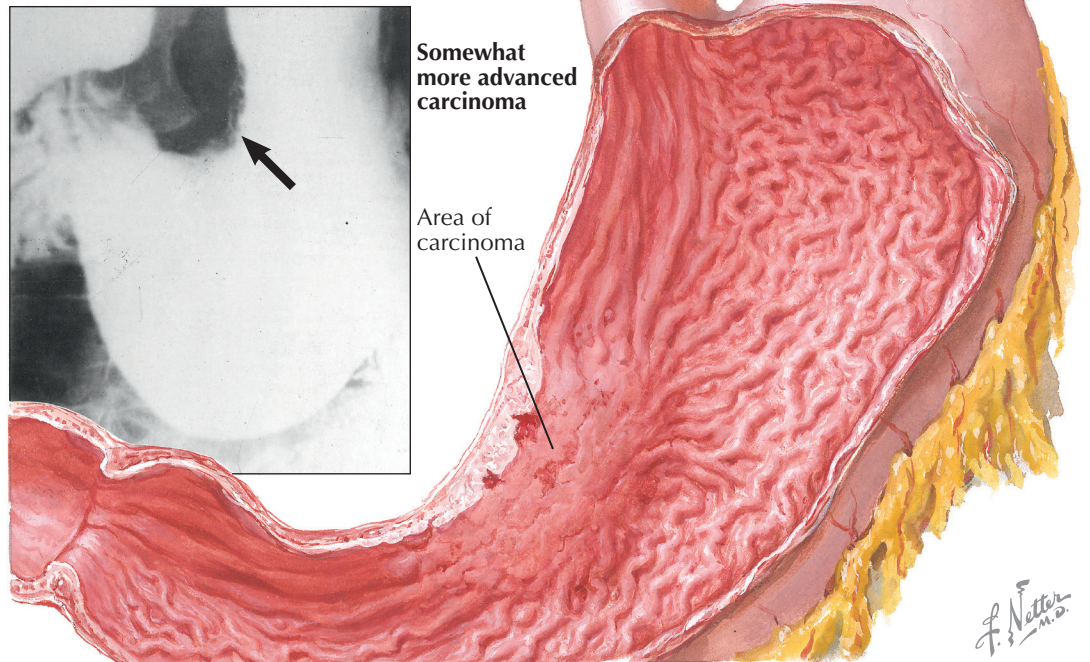
CARCINOMA OF STOMACH

(Continued)

in the direction of the major curvature. Because the tumors have a marked tendency to bleed once they have reached a certain size, severe chronic anemia or a sudden hemorrhage may give the first late clue to their existence.

The cardiac carcinoma often exceeds the bounds of the stomach, either by submucosal infiltration or by more superficial extension, and narrows the cardiac orifice or even the most distal portions of the esophagus. In such instances, it is difficult to differentiate by x-ray or even endoscope a cardiac carcinoma from primary cancer of the distal esophagus. This question may sometimes be decided by endoscopic biopsies with evaluation by a pathologist. Otherwise, the x-ray diagnosis of cancer in the upper part of the stomach is relatively easy, particularly if the growth has altered the anatomic relation of stomach and esophagus. If a stenosis is present, the adjacent portion of the esophagus will be dilated and entry of the barium meal into the stomach will be delayed. When doubts exist as to the diagnosis, the age of the patient, the past history, and endoscopic results may help to exclude achalasia and other benign stenotic lesions (esophagitis, peptic esophageal ulcer, strictures deriving from corrosion). If passage through the cardia is not disturbed, the tumor may be overlooked, particularly if one fails to examine the fundic region. Occasionally, a fundic carcinoma may be flat and infiltration may have proceeded so superficially and broadly that the gastric contour is altered very little.

Surgically, the cardiac carcinoma is best approached by a left thoracotomy or thoracoabdominal incision, because these approaches provide space for additional resection of the esophagus if necessary. Tumors of the fundus, located at a reasonable distance from the cardiac orifice, can be handled through the abdominal approach, because a subdiaphragmatic transection of the esophagus seems to fulfill the requirements of a radical removal of the neoplastic tissues. Should doubts arise during operation that the subdiaphragmatic esophageal resection is adequate, the field can be widened by prolonging the incision into the thoracic wall and the diaphragm, or by continuing the operation by means of a separate thoracotomy. The distal portion of the stomach should



not be removed unless absolutely necessary, because of the extension of the tumor. The physiologic significance of preserving a segment of the stomach has been demonstrated experimentally as well as clinically.

EARLY CARCINOMA OF STOMACH

Some gastric cancers start with a relatively sharply circumscribed area of infiltration, spreading superficially

on an almost even level, without polypoid proliferation and showing little, if any, ulceration. Of the numerous pathologic-anatomic forms in which carcinoma of the stomach can make its appearance, this is the one that most often escapes early clinical recognition, because it leaves the mucosal pattern and the contour of the stomach unchanged for a long time, until the malignant growth has involved a large area. In the early stages, this type expands only within the mucosal layer; then it

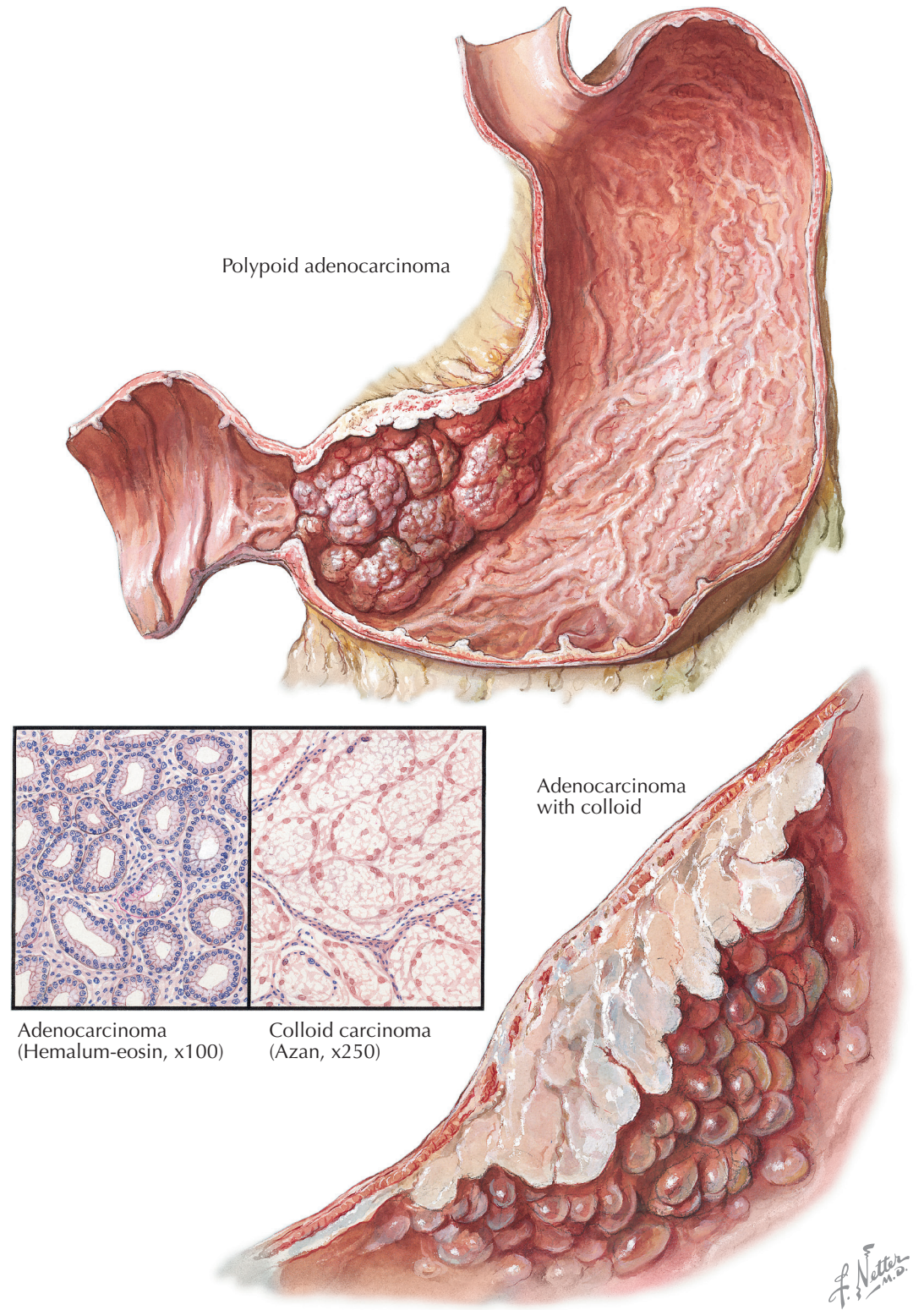
ADENOCARCINOMA OF STOMACH

CARCINOMA OF STOMACH
(Continued)

seizes the submucosa and only much later encroaches upon the muscular coat. Its most frequent location is the lesser curvature between the pylorus and the angular incisure. Irregular flattening and breaks in the mucosal folds; distortion of the rugae, particularly where they begin and end; more or less frank epithelial defects; and, sometimes, small bleeding areas of erosion are the macroscopically visible characteristics of this slow-growing tumor in its early stages. As time passes, local inflammatory reactions and the extension of the neoplasm in the muscularis takes place. On x-ray examination, first a scarcely noticeable but then an increasingly striking stiffening of the region appears. The normal peristaltic waves are interrupted in the rigid segment of the gastric wall. A *polygram* of the peristaltic waves by repeated roentgenographic views of several phases of a peristaltic movement may be informative in these cases. In view of the fact that the contour of the organ is not changed either by the formation of an ulcer crater or by endophytic growth, only the most careful fluoroscopic examination of the condition of the gastric wall or a series of spot films or a videofluoroscopy will permit one to show this type of gastric carcinoma.

ADENOCARCINOMA OF STOMACH

From the histopathologic point of view, the most frequent malignant growth in the stomach is adenocarcinoma. Its macroscopic appearance, as the surgeon or the pathologist sees it, depends essentially upon the time or the developmental stage at which it happens to be recognized. In its early stages, it may be a relatively small, cauliflowerlike mass only a few centimeters in diameter, which projects into the lumen. Unfortunately, however, it reaches far larger dimensions (though still being well circumscribed) before causing local symptoms and before having metastasized to more distant structures. In any event, the size of the tumor alone is not indicative of the spread to neighboring organs. If it grows in the prepyloric area, as do about two thirds of gastric cancers, it may bring about early signs of obstruction, gastric enlargement, and disturbances of the motoric function of the stomach, which lead to its discovery. Macroscopically visible invasion of the

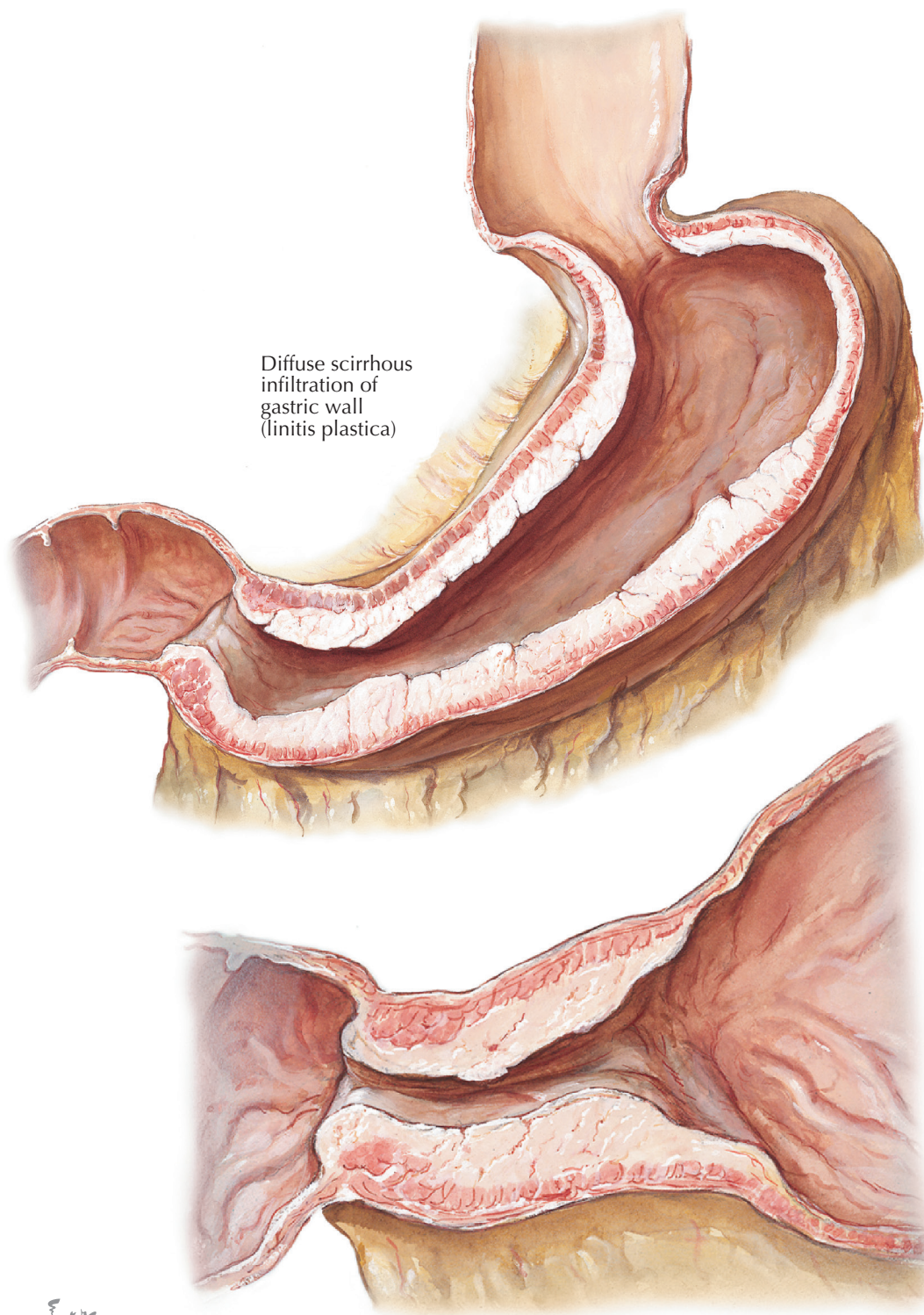


pylorus proper or of the duodenum by a gastric adenocarcinoma is an extreme rarity.

Gastric adenocarcinoma usually arises from a broad base. Less frequently, a papillary adenocarcinoma arises from a polyp or pedunculated adenoma and invades the gastric wall through the stalk. Some adenocarcinomas assume on their surface a *polypoid* or *fungating appearance*, with necrotic and ulcerating foci. On the cut section, this “vegetative” type of carcinoma, as it has

been called, presents a yellowish, solid mass in a gray fibrillar stroma. The histologic architecture of the adenocarcinoma may sometimes exhibit the typical columnar cell arrangement, with formation of glandular spaces, but it is usually more complicated and varies considerably. Atypical tubular glands may replace the normal mucosal pattern, penetrating into the muscularis mucosae or spreading from the submucosa as far as the serosal coat. The nuclei of the tumor cells stain

SCIRRHUS CARCINOMA



CARCINOMA OF STOMACH

(Continued)

distinctly darker than do those of the normal surrounding glands. At times, the tumor consists only of closely grouped alveoli with cylindrical and cuboidal cells and hyperchromatic nuclei. The cells lining these alveoli may, in some cases, contain substantial amounts of mucus, and, occasionally, the entire tumor may be replaced by gelatinous or slimy *colloid material*, in which only a few embedded cancer cells may be found. In such instances, the displaced nuclei and overextended, ruptured, or disintegrated cells in this mucinous matrix may create a most *complex histologic picture*.

LINITIS PLASTICA

Linitis plastica, also known as Brinton disease, scirrhous carcinoma, or leather bottle stomach, is a morphologic variant of gastric cancer with a diffuse and infiltrating form. This rare type of stomach cancer begins in the lining of the stomach and spreads to the muscles of the stomach wall. This causes the wall to become thick, hard, and rubbery, which leads to trouble in digesting food. Another cause of linitis plastica is metastatic infiltration of the stomach, particularly by breast or lung carcinoma.

Linitis plastica produces a diffuse thickening of all layers and involves a large part of the gastric wall (sometimes, the entire wall), which becomes contracted and rigid. The scirrhous malignant lesion usually begins in the pyloric canal and may, in some cases, remain limited to this region, where it may soon cause signs of obstruction, because the profuse growth of its fibrotic components markedly reduces the lumen. The same phenomenon takes place over the whole gastric cavity, when the scirrhous growth has expanded extensively over the entire lining. The mucosal folds become immobile and inflexible, while simultaneously, as a result of the abundant formation of fibrous tissue, the whole organ shrinks, assuming a shape that has been described as the *leather bottle stomach*.

Histologically, nests of epithelial cells are scattered in dense fibrous tissue, which leaves nothing of the normal gastric structures. The number of recognizable malignant cells is gradually reduced, and, in the advanced stages, it is difficult to demonstrate their presence except by the most painstaking microscopic study. In some cases the fibrotic reaction has gone so far as to

make recognition of the original nature of the process practically impossible. In view of such proliferation of connective tissue, it is not surprising that the primary cause was formerly considered to be a chronic reactive inflammatory process and received, accordingly, the designation *linitis plastica*.

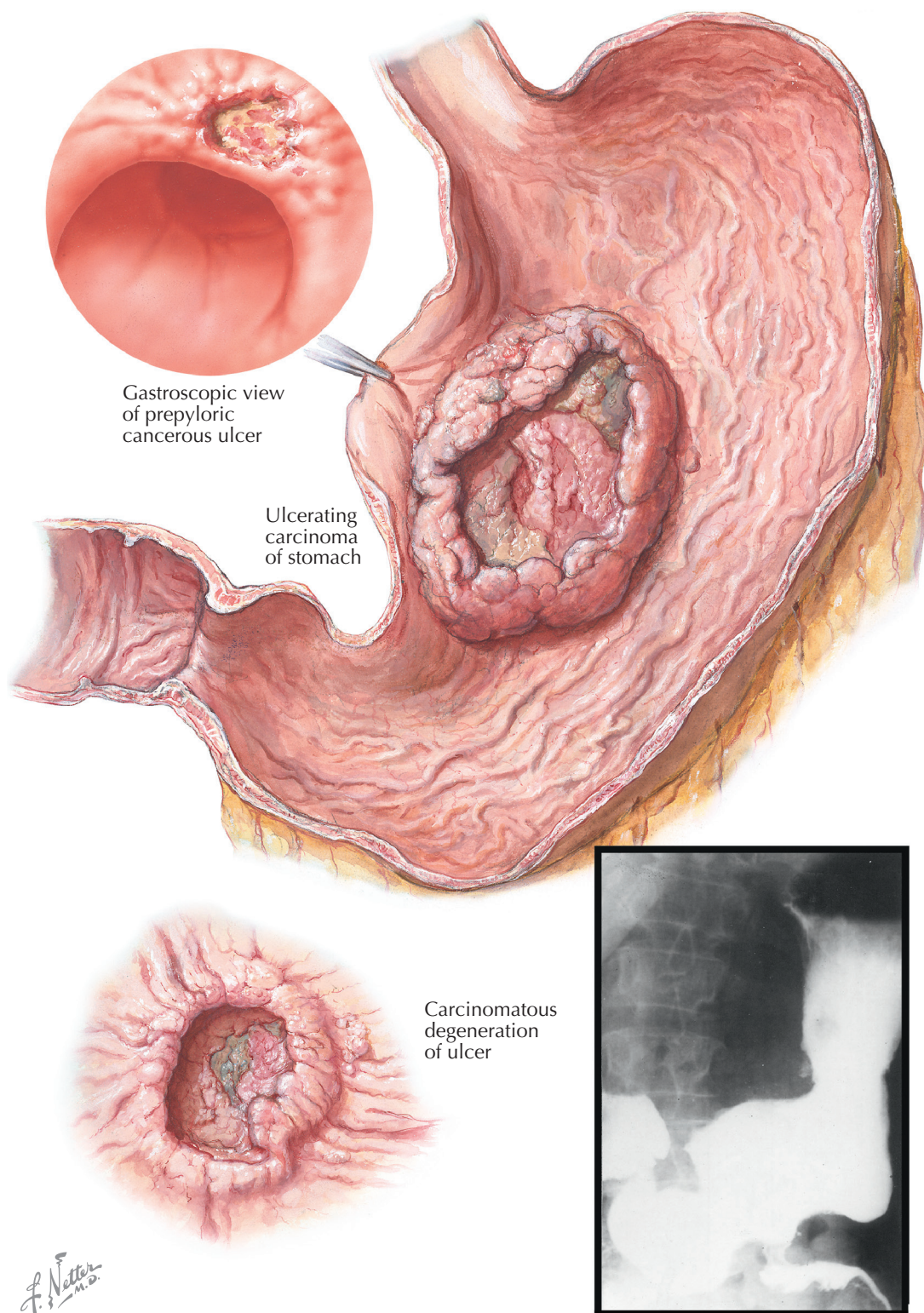
The roentgenographic appearance of linitis plastica, or scirrhous carcinoma, varies, of course, depending upon the extent to which the gastric wall has become

involved. If limited to the pyloric region, a localized area of narrowing, distinct irregularities of the contour, and the disappearance of the normal mucosal markings leave no doubt as to the diagnosis. With the *fibrotic process* sufficiently *advanced at the pyloric canal* to cause a more or less complete obstruction and the more proximal parts of the wall still maintaining their normal structure and extensibility, the stomach is markedly dilated and can retain food ingested during the previous

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Malignant infiltration limited to pylorus

ULCERATING CARCINOMA



CARCINOMA OF STOMACH

(Continued)

24 hours or even over a longer period of time. If, however, the neoplasm has spread over a larger segment or, as happens not infrequently, over the entire inner aspect of the stomach, the cavity of the stomach presents itself as a narrow tube with no mucous membrane pattern visible. The *contour* in such cases may be *erratically distorted*, and the barium meal rushes through the organ because of the rigidity of the pylorus, which, under these circumstances, is permanently opened. Gastric peristalsis in these patients is conspicuously absent. Because the obstruction in advanced linitis plastica is located at the cardia, it is the esophagus that eventually becomes dilated.

With x-ray findings as clear as those described above, the diagnosis of scirrhous carcinoma presents no difficulties, and laboratory data, such as achlorhydria, hypochromic or hyperchromic macrocytic anemia, or occult blood resulting from the destruction of the glands or from erosions, provide little more than mere additional supporting or confirming information. Upper endoscopy, at times difficult to perform because of the rigidity and lack of air in the stomach, may help establish the diagnosis, although the endoscopic picture of an infiltrating carcinoma may now and then resemble that of a lymphoma or hypertrophic gastritis, necessitating a biopsy for differentiation. The unfortunate feature of the situation, however, is that these characteristic x-ray pictures are seen only in a late stage of the disease when the presence of lymph node metastases can be expected. Symptoms develop rather insidiously, and patients come for medical care at a time when total gastrectomy, the only sensible treatment for this condition, can scarcely be more than palliative. The prognosis may become more favorable for the infiltrating type of carcinoma, as for other types of cancer of the stomach, when the methods for early recognition improve and when institutions such as cancer prevention clinics are more widely used.

ULCERATING CARCINOMA OF STOMACH

Many pathologists separate ulcerative cancer as a special type and consider it the most common form of early detectable gastric carcinoma. Though all forms of cancer of the stomach may become necrotic in parts and

undergo ulcerative degeneration, it is particularly adenocarcinoma and its papillary and polypoid varieties that tend to ulcerate while still relatively small. Necroses and loss of substance on the surface of a diffuse, infiltrating, scirrhous carcinoma are relatively rare and only superficial, whereas the funguslike, proliferating, and more circumscribed (but still broadly infiltrating) neoplasms tend often to become deeply ulcerated by the sloughing of substantial parts of their central

segments, probably because their blood supply cannot keep pace with their rapid growth. In such cases, especially with the early superficially spreading type, it may be extremely difficult, if not impossible, to separate the ulcerating carcinoma diagnostically from a benign chronic, callous, and penetrating peptic ulcer. The issue is further complicated by the fact that a not negligible percentage of ulcers that were originally benign may undergo *malignant alteration*.

CARCINOMA OF STOMACH (Continued)

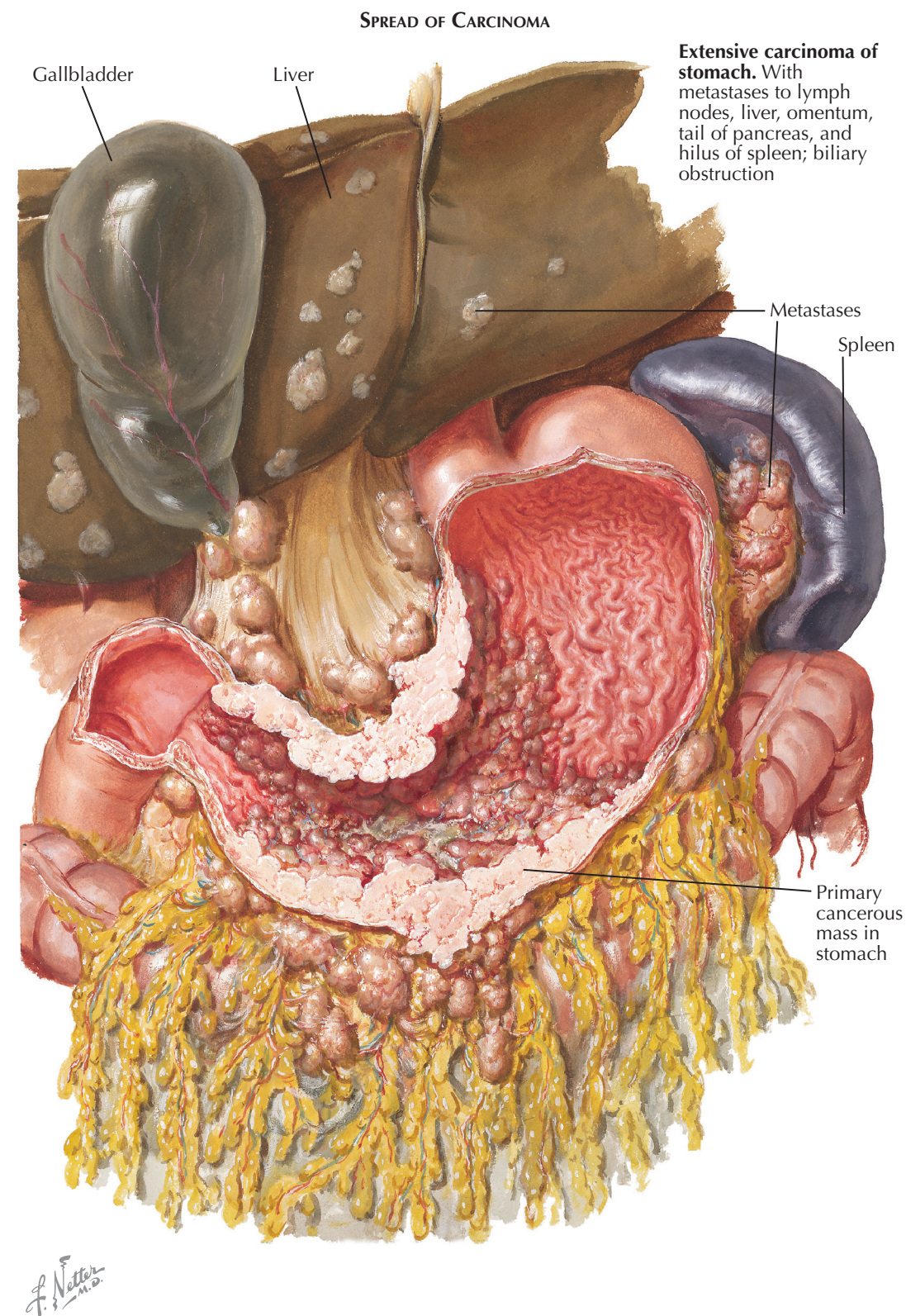
The functional disturbances brought about by cancer of the stomach depend essentially on the tumor's location and size. The great majority of patients feel no discomfort or pain in the early stages and report to their physician only when the neoplasm has reached dimensions that cause obstruction of the pylorus or cardiac orifice or reduction of the entire gastric lumen or secreting surface. At this time a gamut of manifestations, from vague epigastric discomfort, nausea, and anorexia to weight loss and cachexia, may be present, pointing to a serious digestive dysfunction. If the tumor happens to invade the nerves, pain may become one of the early or actually the earliest symptom. In such cases, as well as with manifestations of an ulcerating tumor, the physician faces the most difficult problem of differentiation between a cancer and a benign ulcer. In any event, whatever the symptoms and whenever they appear, it has been estimated that at least half of the patients with gastric carcinoma do not seek medical attention until the tumor has extended beyond the stomach.

SPREAD OF CARCINOMA OF STOMACH

All types of carcinoma of the stomach either spread by direct extension to neighboring organs or metastasize by means of the lymphatics or bloodstream. Some types have a greater tendency and some (e.g., scirrhous carcinoma) a lesser tendency to produce metastases. The regional lymph nodes become involved, sometimes very early and usually, though by no means always, in a definite sequence. With the lesser curvature being, to a certain degree, the preferred site, the lymph nodes of the stomach and their drainage system along the left gastric artery and the coronary vein are those first and most frequently affected. A rather serious prognostic significance must be attached to an early *involvement of the nodes in the pyloric area*, including the suprapancreatic nodes and those near the hilus of the liver, which excludes any possibility of radical removal of the malignancy. Secondary growth of malignant tumor cells in the *lymph nodes of the prepyloric, pyloric, and pancreatic regions* and in the *hepatoduodenal ligament* may be accompanied clinically by icterus, as a result of an obstruction of the common bile duct, subsequent biliary stasis, and dilatation of the gallbladder (*Courvoisier law or sign*). The *liver* is held as a site of predilection for *metastases* of gastric cancer, either by direct spread or through the lymphatic routes just mentioned. It is possible, but probably not common, for cancer cells to enter the liver by way of the portal circulation. Similarly, though less frequently, metastases develop in the lower part of the esophagus, colon, pancreas, and gallbladder.

Metastatic involvement of the lymph nodes along the greater curvature, in the gastrocolic ligament, and in the *omentum majus* occurs less regularly than in those structures along the lesser curvature. Occasionally, the cancer cells are carried via celiac lymph nodes to the thoracic duct and the mediastinal and supraclavicular lymph nodes (Virchow node).

Hematogenic metastases in lung, bone, and brain (in that order of frequency) are relatively rare and are encountered, of course, only in far-advanced cases.

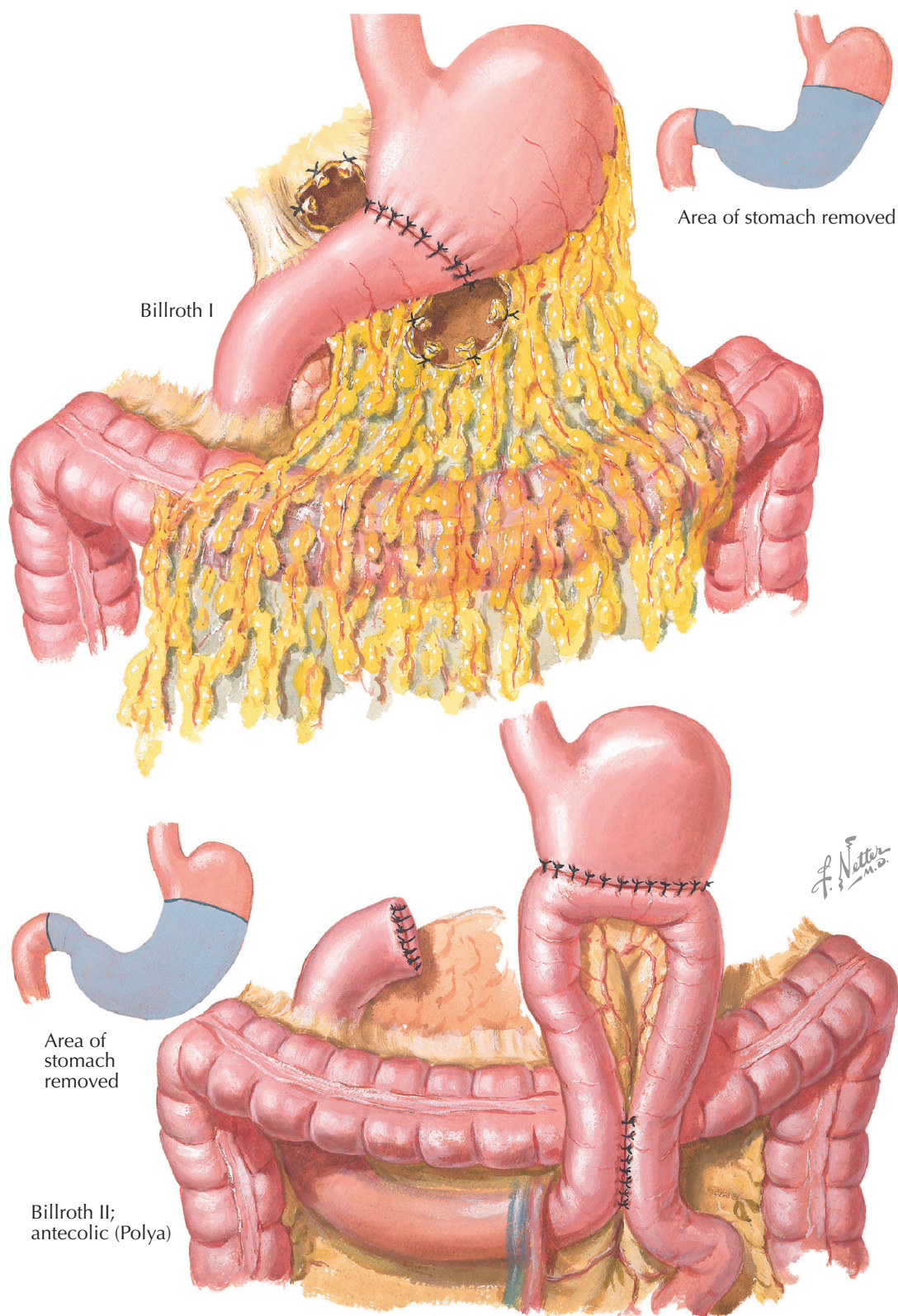


The direct transplantation of aberrant *cancer cells* upon the *peritoneum* represents a special type of spread. It requires complete penetration of the stomach wall and, thus, is again a phenomenon of an advanced stage of gastric cancer. Once the serosa has become involved, cancer cells may be set free and may settle on the surface of any organ within the peritoneal cavity. The ovaries seem to be the most frequent site, sometimes the only site of such implanted metastases, which, in

this organ, develop into a histologically rather characteristic secondary neoplasm known as *Krukenberg tumor*. If conditions permit, the simultaneous resection of the primary tumor and the ovarian metastases seems justified and worth serious consideration.

Another, certainly not infrequent, site of metastases is the pelvic peritoneum, where they may project into the rectum as a shelflike structure (rectal shelf of Blumer) and can be felt on rectal examination.

PARTIAL GASTRECTOMY AND BILLROTH ANASTOMOSES



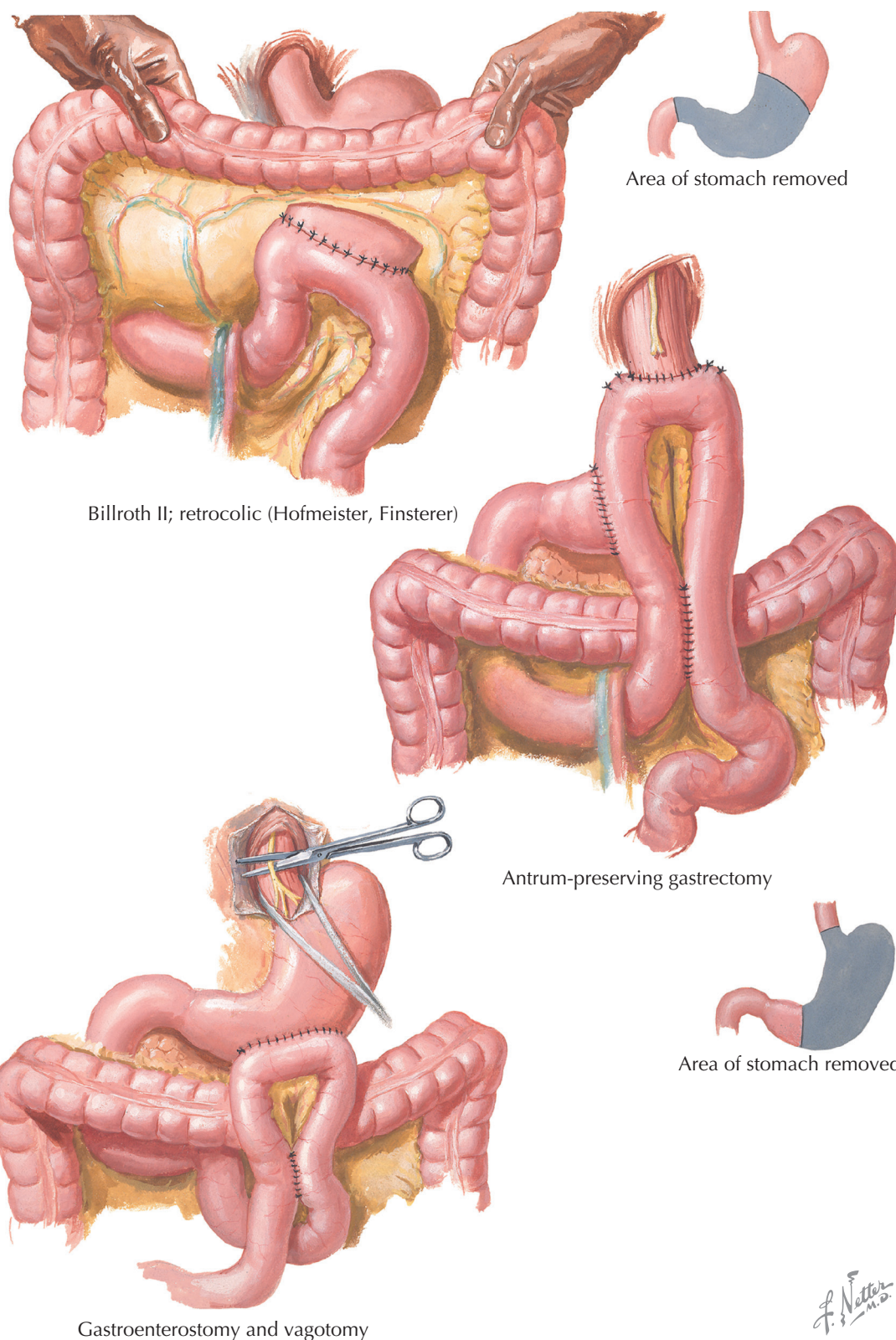
PRINCIPLES OF OPERATIVE PROCEDURES

Treatment of a peptic, gastric, or duodenal ulcer begins with medical management (diet, antacid therapy, anti-secretory drugs). No rule of thumb can be given or used to fix the period of time during which medical treatment should be continued in the hope of improvement in symptoms. A great variety of individual factors must be considered before concluding that further medical efforts to regulate diet, habits, and gastric secretion will not be helpful. In general, however, the physician and patient should avail themselves of the benefit of consultation with the surgeon if the symptoms do not abate after several months of adhering strictly to sound medical therapy. Failure of response with a well-planned regimen, repeated recurrences of severe symptoms, intractable ulcer pain, lack of endoscopic evidence that the ulcer has not completely healed after a few months (even though marked subjective improvement is noted), persistence of blood in the stool, and any other signs of a threatening complication are fairly universally accepted as indications for surgical intervention.

When one suspects that a gastric lesion is not a benign process, a surgical consultation is helpful. The precise operative procedure in the presence of an established, or even suspected, malignancy depends largely upon the size, site, and extent of the lesion. In most cases, if an extensive procedure is at all feasible, the situation will require nothing short of a subtotal or total gastrectomy, leaving the fundus if the tumor occupies the antrum or the distal part of the corpus, and leaving the antrum when the tumor is confined to the most proximal gastric regions.

The surgical procedure of choice for a gastric or duodenal ulcer is a *subtotal gastrectomy*, by which two thirds to three quarters of the distal portion of the stomach is removed, aiming to reduce the acid-secreting mucosa to such a degree that the gastric juice reaches a state of anacidity or at least hypoacidity. Because only complete removal of the entire antrum can guarantee a permanent ablation of acid production, the distal line of the resection must lie beyond the pylorus.

The Viennese surgeon Billroth was the first to perform a partial gastrectomy, which included the pylorus and connected the distal end of the remaining stomach with the open end of the duodenum. The mobilization of the duodenum, necessary for such an end-to-end gastroduodenostomy, can often be obtained tension-free without technical difficulties. This type of operation, known as the *Billroth I procedure*, deserves preference over all other operative procedures, because



PRINCIPLES OF OPERATIVE PROCEDURES (Continued)

with it the physiologic pathway for food transport is preserved and the sequence of the digestive processes is less disturbed than with any other procedure. Execution of the Billroth I procedure, however, is restricted by the prime necessity of a healthy duodenal cuff wide enough for the end-to-end anastomosis. Consequently, this type of operation is technically precluded, in many cases, by fibrotic or scarring alterations of the duodenal wall.

Faced with cases in which the first type of procedure was not feasible, Billroth developed another type of gastrectomy, known as the *Billroth II procedure*, in which, after closing the duodenal opening, he connected the stump of the stomach to a loop of jejunum. Such a gastrojejunostomy can be constructed either in front of the transverse colon or in retrocolic fashion, by pulling the needed length of the jejunum upward through a slit made in the transverse mesocolon. In the antecolic procedure, it has proved imperative to provide a side-to-side anastomosis of the afferent to the efferent limb of the jejunum at some distance from the stomach. This *Braun anastomosis* prevents stasis in the afferent limb of the loop and, thereby, the danger of a blowout of the bypassed duodenal stump.

Bilateral *vagotomy* (i.e., the severing of both vagus nerves at the level of the juxtacardiac portion of the esophagus) aims at eliminating or reducing the cephalic

phase of gastric secretion. The hopes once entertained that this simple procedure would permanently cure an ulcer have not been fulfilled. As experience has shown, the effect of vagotomy on acid production is often inadequate and, in most cases, only transient. Furthermore, this severance of the nervous pathway tends to induce a persistent pylorospasm and dyskinesia of the small and

large intestine, resulting in a severe spastic constipation. If vagotomy is performed as the sole procedure to relieve ulcer symptoms, because for one reason or another the surgeon cannot carry out a subtotal gastrectomy, it is always imperative to perform at least a gastrojejunostomy or pyloromyotomy to prevent a hold-up of the gastric evacuation.

BARIATRIC SURGERY

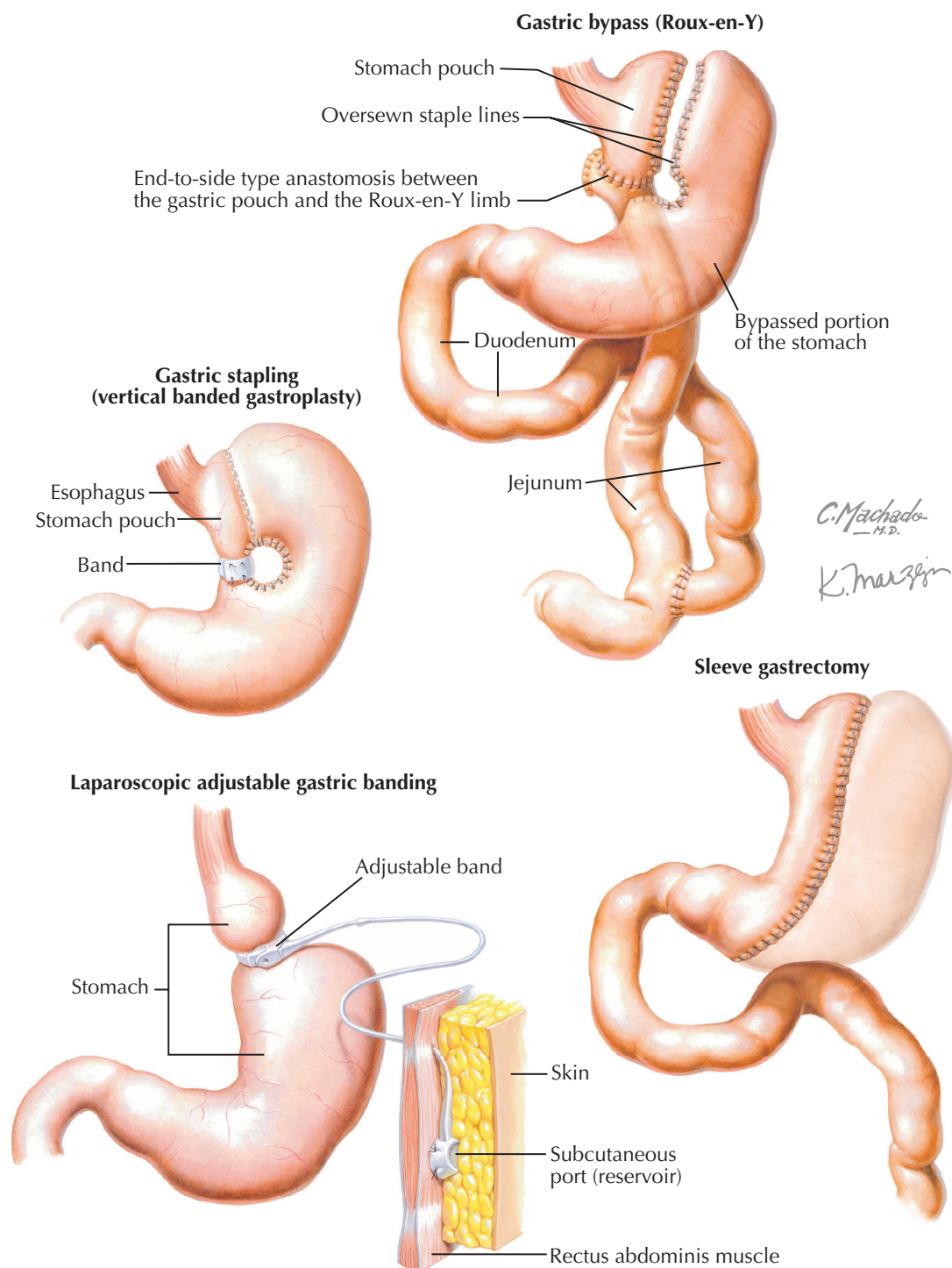
Obesity is associated with a decrease in the quality of life as well as the life expectancy. Although both medical therapy and caloric reduction remain the first-line therapies for obesity, bariatric surgery is the most effective therapy for sustained weight loss. Bariatric surgery is considered for people with a body mass index greater than 40 kg/m², or for those with a body mass index less than 40 kg/m² and obesity-related diseases. Bariatric surgery involves surgical manipulation of the gastrointestinal tract to alter normal anatomy and physiology to accomplish weight loss. Weight loss has been described through two mechanisms: restriction of food intake and malabsorption of ingested food. Additionally, the neurohormonal effects of bariatric surgery are now recognized as an important mechanism for both weight loss and improvement in comorbid conditions. Along with weight loss, bariatric surgery can improve comorbidities, including diabetes mellitus, hypertension, hyperlipidemia, obstructive sleep apnea, and GERD. Relative contraindications include poorly managed psychiatric disease, a history of eating disorders, poor compliance with dietary modifications, or high concern about the patient's ability to comply with medical follow-up.

The most common bariatric surgeries currently performed are (1) laparoscopic adjustable gastric banding (LAGB), (2) sleeve gastrectomy, (3) Roux-en-Y gastric bypass (RYGB), and (4) biliopancreatic diversion with duodenal switch (BPD/DS). Operations are typically performed laparoscopically, unless intraoperative complications or technical difficulties require conversion to an open procedure.

LAGB involves placing an inflatable band along the proximal stomach, approximately 20 to 30 cm from the gastroesophageal junction at the angle of His. The anterior surface of the stomach is sewn over the band to secure it in place. Tubing with an attached port is connected to the band and placed in the anterior abdominal wall to control inflation. Postoperatively, the band is adjusted based on weight loss. Although this technique is effective, the amount of weight loss that results is less than with the other three types of bariatric surgeries. Complications can include band slippage, band erosion, prolapse of the distal stomach into the band, or malfunction of tubing. The popularity of this procedure has decreased because sleeve gastrectomy produces more weight loss.

Sleeve gastrectomy has rapidly become the most popular surgery for obesity. It involves a gastrectomy from the antrum to the angle of His, using a stapled division of the stomach. A bougie or endoscope is used during the operation to ensure that the gastric sleeve is of adequate diameter. The explosive increase in frequency of sleeve gastrectomies is due to the increased weight loss produced compared with LAGB, the technical ease of the surgery, and the decreased risk of nutritional deficiencies compared with RYGB. Complications include a postoperative leak along the proximal staple lines and continued GERD. Patients with preexisting GERD are often referred for RYGB over sleeve gastrectomy.

RYGB remains a popular procedure despite a transition in the field of bariatric surgery from open to laparoscopic or robotic procedures. For the procedure, the jejunum is divided approximately 50 cm from the liga-



ment of Treitz. The section of jejunum in continuity with the stomach is now the biliopancreatic limb. The other half of the small bowel forms the Roux limb. An anastomosis is created between the biliopancreatic limb and the Roux limb. A small gastric pouch is created in the proximal stomach. The Roux limb is anastomosed to this gastric pouch, completing the procedure. Complications include anastomotic leak or stenosis, marginal ulcers, and nutritional deficiencies due to malabsorption. RYGB is second only to the BPD/DS in efficacy for weight loss.

BPD/DS is the most effective procedure for weight loss and is therefore considered for morbidly obese patients. First, the greater curvature of the stomach is resected, as in a sleeve gastrectomy. The ileum is divided approximately 250 cm from the ileocecal valve.

The duodenum is divided, and the distal ileal segment is anastomosed to the duodenal segment attached to the stomach. The other limb, which carries pancreatic enzymes, is anastomosed to the terminal ileum. Although it has been highly effective for weight loss, BPD/DS is performed in only a minority of people undergoing bariatric surgery because of its technical difficulty and complication rate and the associated extreme malabsorption and large stool output.

The short-term complications are wound infection and surgical leak, bleeding, deep venous thrombosis, and pulmonary embolism. The late complications include cholelithiasis, short bowel syndrome, stomal stenosis, marginal ulcers, nutritional deficiencies, and dumping syndrome. The importance of dietary instructions and follow-up cannot be overemphasized.

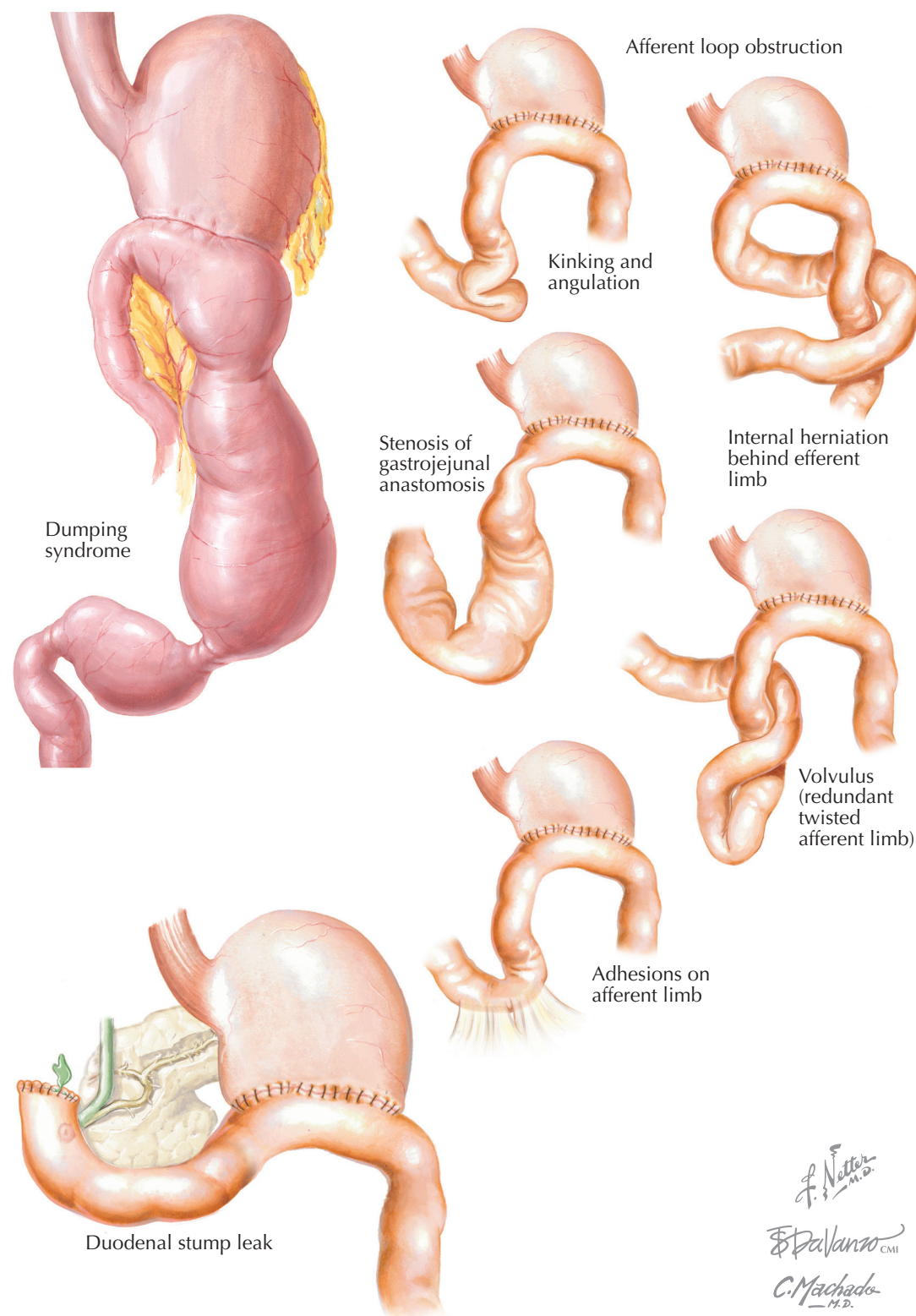
POSTGASTRECTOMY COMPLICATIONS

In patients who have undergone some form of gastrectomy, the loss of gastric function may have serious consequences for health. The stomach performs functions that may not adequately occur if it is partially or fully removed. Complications seen after these surgeries can occur early or late and are related to changes in reservoir function, vagal denervation, or abnormalities in surgical reconstruction.

Surgical complications include *anastomotic leaks* and *hemorrhage*, which more commonly occur at the gastrojejunal anastomosis. In Billroth II surgeries, duodenal stump leaks can occur in up to 5% of patients. This complication occurs after dissection and suturing of the duodenal stump and is due to abnormal traction or ischemia in the region of the stump. Leaks usually present with abdominal pain, leukocytosis, and sepsis. All cases of leaks can be diagnosed by an upper gastrointestinal series and show extravasation of contrast. Management includes nothing by mouth, nasogastric decompression, and antibiotics. Surgical revision may be needed if conservative treatment is ineffective. Another complication that occurs after 1% of Billroth II surgeries is *afferent limb syndrome*, a mechanical complication due to kinking, herniation, or volvulus of the afferent limb; bezoar, ulceration, or tumor recurrence can also precipitate this situation. Afferent limbs longer than 30 cm and antecolic position are risk factors. Patients often present with severe abdominal pain and severe vomiting 30 to 60 minutes after eating, although jaundice, cholangitis, pancreatitis, or duodenal stump leak can rarely occur. Elective or emergency surgical revision is needed to fully alleviate the symptoms.

Dumping syndrome is also a common complication and occurs in some form in 25% to 50% of postgastrectomy patients. Early dumping syndrome occurs within an hour of ingestion of hyperosmolar meals, leading to rapid fluid shifts from the intracellular space into the lumen of the jejunum. Patients often present with nausea, abdominal fullness, dizziness, diaphoresis, tachycardia, and diarrhea. Late dumping syndrome occurs 1 to 3 hours after ingestion of food and is due to rapid absorption of hyperosmolar food leading to hyperglycemia, with subsequent hyperinsulinemia and reflex hypoglycemia. Patients with late dumping syndrome present differently, with loss of consciousness and tremor. Upper gastrointestinal series reveal rapid emptying and complete evacuation of contrast material from the esophagus and remnant stomach, resulting in a dilated efferent jejunal limb. The mainstay of treatment in both early and late dumping syndrome is modification of oral intake, with small, frequent, slowly chewed meals that are low in carbohydrate and higher in protein and fiber content. Separating the intake of liquids from solids by at least 30 minutes is also advised. Medical therapy aimed at slowing down the intestinal transit time can be helpful if conservative measures are ineffective.

The important vagal nerve controls gastric accommodation and motor function of the stomach, including gastric emptying. Unintended or traumatic *injury to the vagus nerve* can lead to local diarrhea, which may be unrelated to dumping syndrome. Bloating or abdominal pain due to gastric stasis can also be a presenting complaint. Medical therapy aimed at improving motor



function is the mainstay of therapy, with surgical therapy reserved only for symptomatic patients who do not respond to conservative therapy.

Other complications of gastrectomy surgery include *anemia* and *osteoporosis*. Anemia may occur as a result of iron malabsorption or vitamin B₁₂ deficiency. Iron deficiency occurs as a result of reduced production of acid which leads to an inability to effectively convert dietary iron into a form easily absorbed by the small intestine. Vitamin B₁₂ deficiency develops if the proximal stomach

is resected. This part of the stomach produces intrinsic factor, which is a protein that binds vitamin B₁₂ and aids in its absorption within the small intestine. Calcium malabsorption and resulting osteoporosis can also occur in this population. Calcium is absorbed in the proximal small intestine and may not be effectively absorbed if stomach contents rapidly empty into the small intestine. All of these consequences generally occur years after surgery when the body has used up its stores of iron, calcium, and vitamin B₁₂.

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COMPLICATIONS OF GASTRECTOMY (BARIATRIC SURGERY) FOR OBESITY

New procedures for gastrectomy (bariatric surgery) have been developed to reduce the stomach volume and induce weight loss in the obese population. Operations that create a small gastric pouch include the Roux-en-Y gastric bypass as well as the sleeve gastrectomy. Unique complications are specifically related to the type of surgery performed.

In the *Roux-en-Y gastric bypass (RYGB)*, a small gastric pouch containing the cardia and part of the fundus is created that typically can hold 15 to 30 mL of fluid. This pouch has a direct anastomosis with a jejunal limb that is brought up to the pouch. This jejunal limb is generally 75 to 150 cm in length; longer lengths induce malabsorption and a greater degree of weight loss.

Complications from RYGB can be divided into early and late complications. In the early postoperative period, gastric leaks are the most worrisome of the complications and can lead to abscess formation and sepsis. Other early complications include ulcer formation, which generally occurs on the jejunal side of the gastrojejunal anastomosis. The true cause of this type of ulcer is likely ischemic changes within the area, but direct acidic peptic damage to the jejunum is also a possibility. Treatment for jejunal ulceration should include acid-reducing medications in addition to medications that coat the area and reduce direct mucosal damage. Elimination of NSAIDs and tobacco is also necessary.

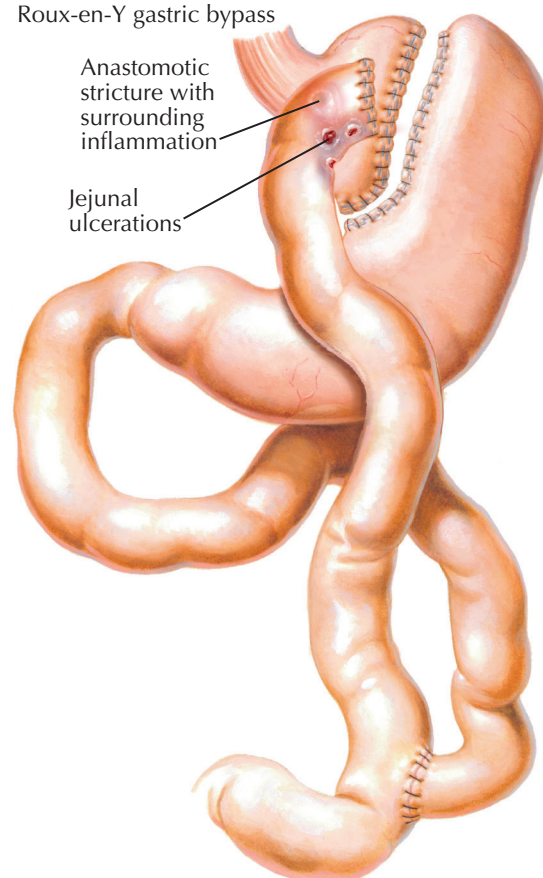
Late complications from RYGB include gastrojejunal anastomotic strictures, which generally occur in patients with early anastomotic ulcerations. Patients often present with perceived dysphagia, nausea, and vomiting or an inability to tolerate their diet. Endoscopy is used for diagnosis, and dilation of the anastomosis is required for treatment and adequate relief of symptoms. Elimination of NSAIDs is necessary to prevent recurrence of ulcers and stricturing. Other late complications include fistula tract formation between the excluded stomach and the gastric pouch or enterocutaneous fistulas.

Another common operation for obesity is *sleeve gastrectomy*, also known as *vertical gastrectomy*. Sleeve gastrectomy is less invasive than RYGB and is often performed by laparoscopy. In this surgery, sutures are placed a few centimeters from the angle of His, with extension to 6 cm from the pylorus, causing a vertical transection of the stomach. The result is a tubular stomach, which causes weight loss by restrictive mechanisms. This surgery is becoming more common in high-risk surgical candidates.

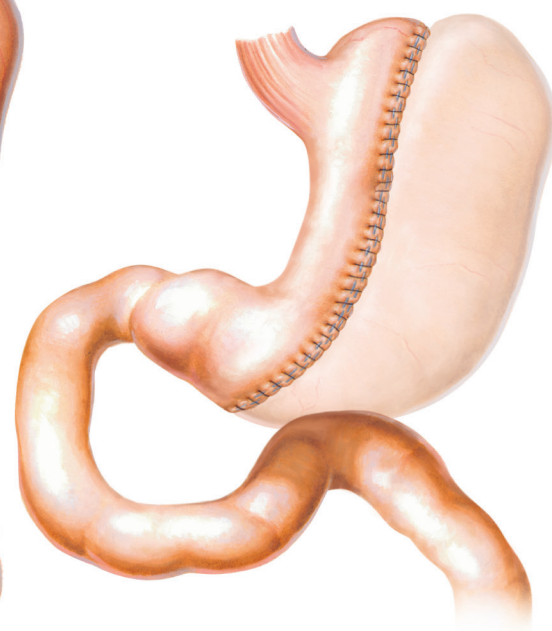
Complications after sleeve gastrectomy commonly involve the staple line and include bleeding, leaks, and strictures. A leak can present insidiously when it is localized. Other leaks lead to vast contamination of the peritoneum and present with fever, tachycardia, abdominal pain, and sepsis. The causes of these leaks are multifactorial; they may be due to local ischemia, mechanical damage, or mucosal injury. Treatment depends on the severity of the leak, the degree of local inflammation, and the duration of time the leak has been present. Typically, subclinical leaks may be treated with nothing per mouth, antisecretory therapy, antibiotics, local drainage, or endoscopic stents. Severe leaks pose several problems because surgery is generally

Obesity gastrectomy surgery complications

Roux-en-Y gastric bypass



Normal gastric sleeve



Kinked gastric sleeve



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advised yet local inflammation may prevent appropriate surgical revision. Patients with staple line bleeding present with gastrointestinal bleeding or bleeding into the peritoneum. Endoscopic therapy may be helpful if the bleeding is in the lumen. Other cases require conservative management, drainage, or surgery. Stricture or kinking that may partially or fully obstruct the stomach lumen may occur as a late complication of staple line disruption; improperly placed sutures can also lead to this complication. If the stomach is

partially obstructed, endoscopic stenting may be useful. In refractory cases, surgical correction is needed.

Nutritional deficiencies can be seen following any of the gastrectomy surgeries; typically they are less severe in sleeve gastrectomy patients. These complications include malnutrition involving vitamins such as vitamin B₁₂, folate, iron, and calcium. GERD is uniquely seen in a subset of sleeve gastrectomy patients. Its cause is unclear; treatment with antisecretory agents generally improves the symptoms.